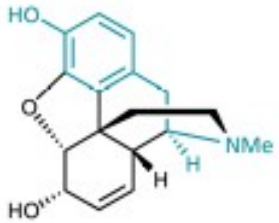
Natural Brain-Pain Killers

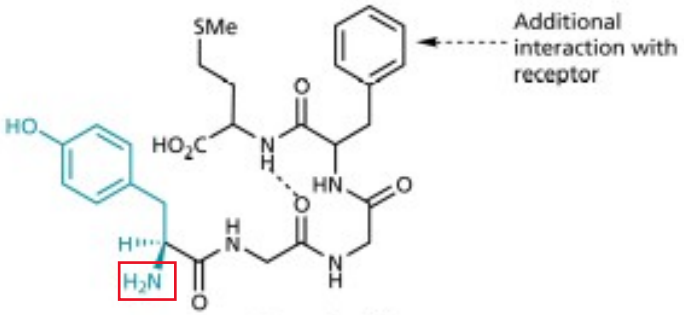
H-Tyr-Gly-Gly-Phe-Met-OH H-Tyr-Gly-Gly-Phe-Leu-OH

Met-enkephalin Leu-enkephalin

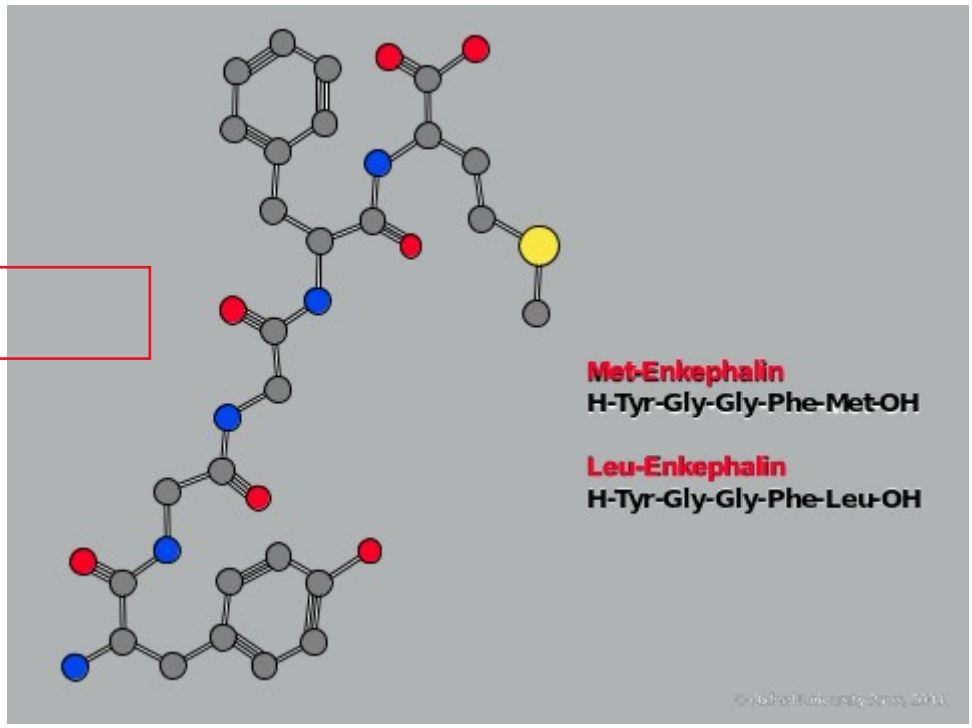
Proenkephalin
Prodynorphin
Pro-opiomelanocortin
} → Endorphins + enkephalins

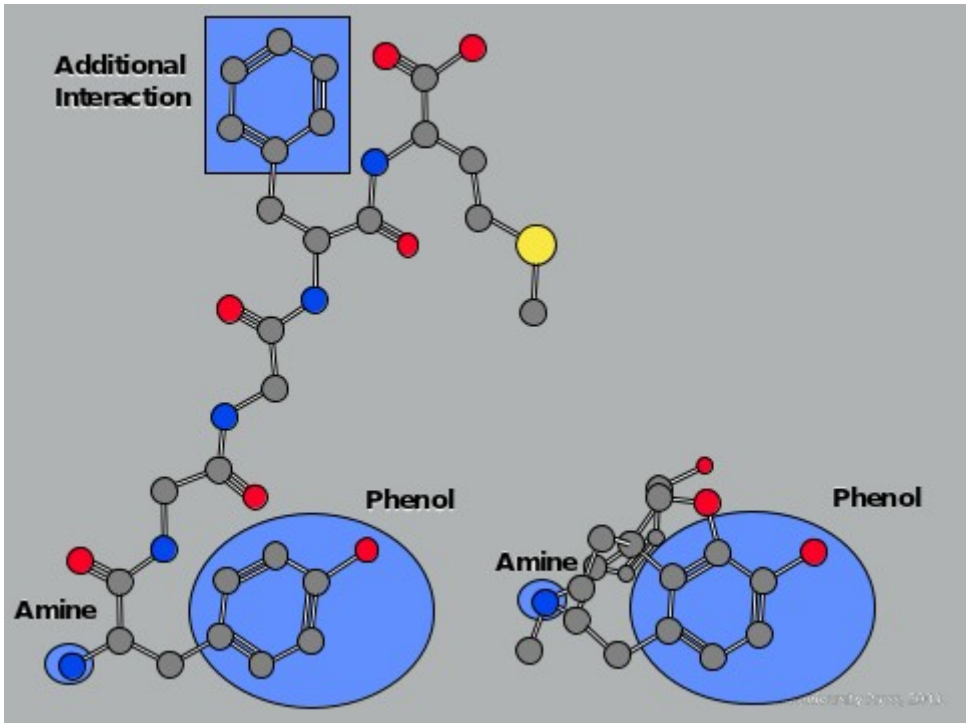


Morphine



Met-enkephalin




Additional
Interaction
Phenol
Amine
Amine
Phenol

NOTES - ENKEPHALINS

Endogenous peptides acting as neurotransmitters in brain

Enkephalin - Greek for 'in the head'

Bind to delta receptor (δ)

Approximately 15 other endogenous peptides of 5-26 AA's (endorphins and enkephalins). All contain Met or Leu enkephalin at *N*-terminus

Biosynthesised from inactive protein precursors (proenkephalin, prodynorphin etc)

Inactived by peptidase enzymes *in vivo* (orally inactive) - hydrolysed between Tyr and Gly

H-Tyr-Gly-Gly-Phe-Met-OH

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SAR

Tyrosine essential for activity (phenol ring and N)

Phenol ring of Tyr thought to be equivalent to phenol ring of morphine

Tyr nitrogen thought to be equivalent to morphine amine

Aromatic ring of Phe important (additional interaction)

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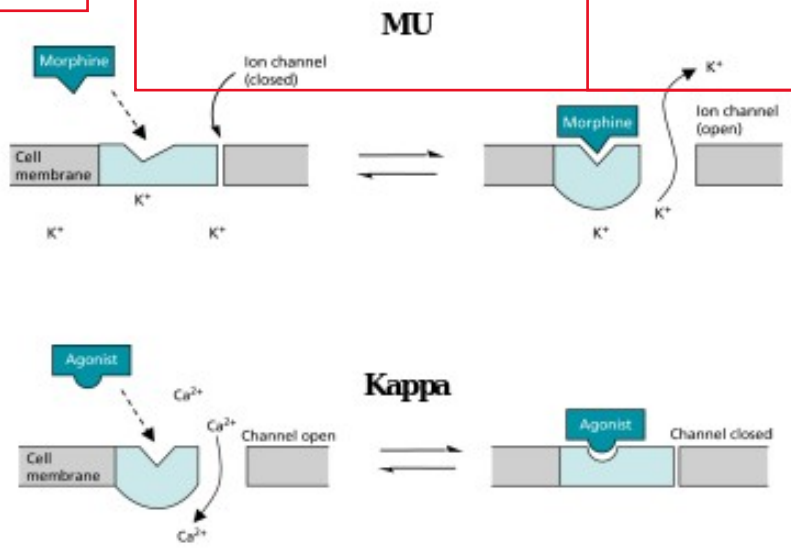
ANALOGUES

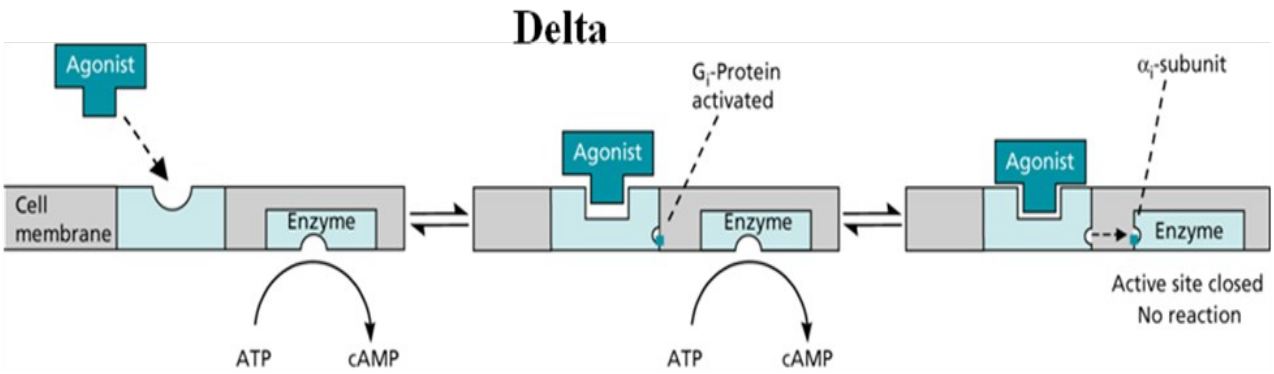
AIM

To synthesise analogues which are stable to peptidases and which would be orally active

STRATEGY

Replace non essential amino acids with unnatural AA's or D-AA's to make enkephalin unrecognisable to peptidase enzymes





Receptor Theories

Multiple Analgesic Receptors

* Three different analgesic receptors (mu, kappa and delta)

* Binding sites for all three receptors contain ionic, hydrogen bonding and hydrophobic regions as proposed by Beckett-Casy

* Activation of all three produce analgesia, but differ in other effects

* All three interact with morphine

* Potential to target drugs selectively

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Mu Receptor (μ)

* Morphine binds strongly

* Activation produces analgesia plus side effects (respiratory depression, euphoria, addiction)

* G-Protein coupled receptor

* μ-Receptor subtypes identified which may allow separation of analgesia from side effects

* μ-Receptors related to all sources of pain stimuli

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Kappa Receptor (κ)

* Morphine binds less strongly

* Activation produces analgesia plus sedation

* Insignificant side effects

* Potential target for safe analgesics (compounds acting as agonists at κ, antagonists at μ and no activity at the δ receptor).

* G-Protein-coupled receptor

* κ Receptors related to non-thermal pain induced stimuli

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Delta Receptor (δ)

* Morphine binds strongly

* Receptor for enkephalins

* Activation produces analgesia plus some side effects

* G-Protein-linked receptor

* δ receptors related to pain induced stimuli from all sources

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Sigma Receptor (σ)

* Activated by some opioid analgesics (e.g. nalorphine)

* Non-analgesic, non-opioid receptor

* Activation produces hallucinogenic effects

* Thought to be responsible for effects of phencyclidine (PCP) (Angel Dust)

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Source of Morphine

- Seed capsule of poppy plants
- Opium is the extract and herbal remedy
- Morphine is the active principle
- Morphine (16%)
- Codeine (4%)

Clinical Use

- Morphine is poorly absorbed orally
- Potential realised with the invention of the hypodermic syringe

Pharmaceutical Press, 2009.

Side Effects

- Respiration
- Nausea
- Pupil constriction
- Constipation
- Euphoria
- Tolerance
- Dependence

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Structure

1923

MORPHINE

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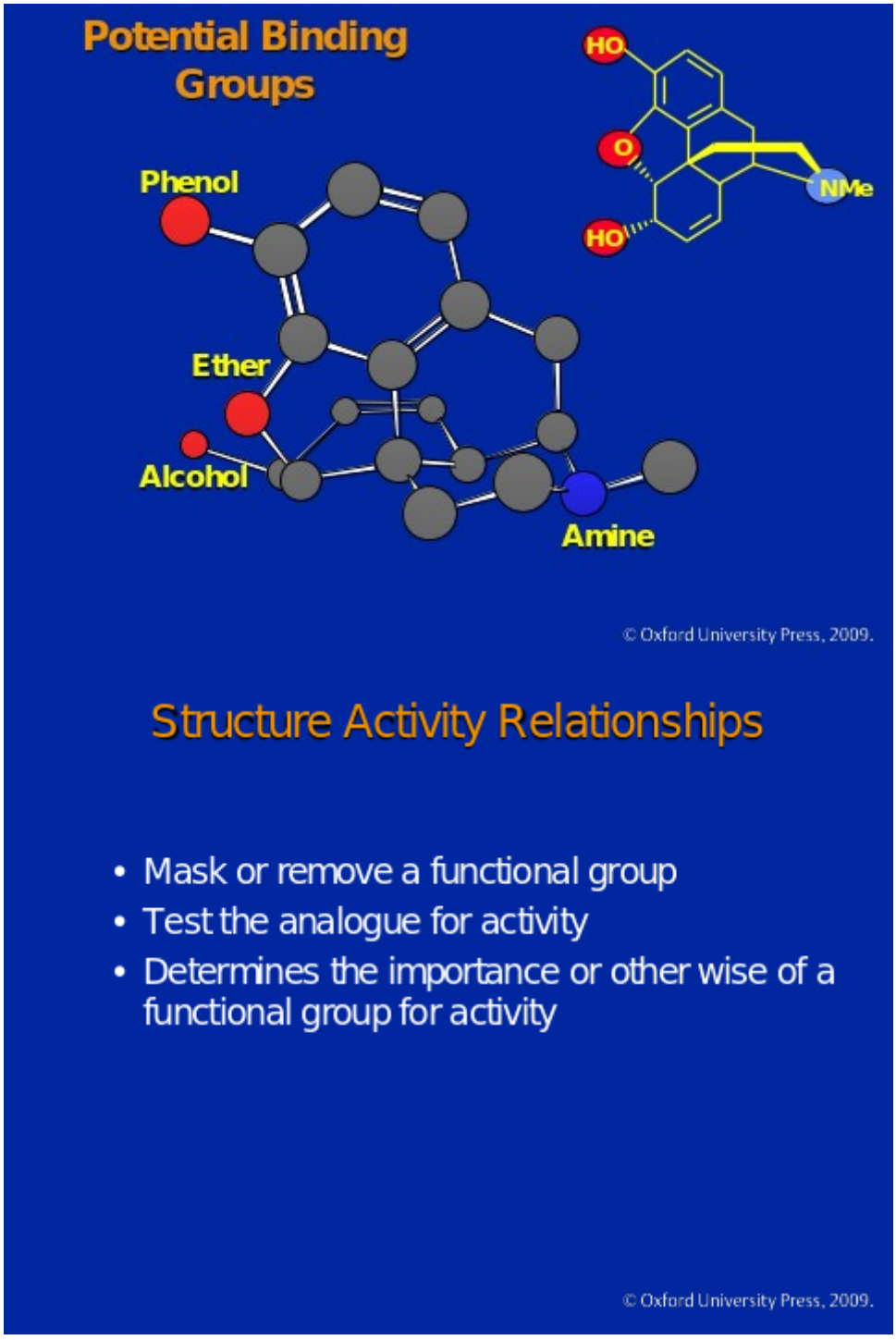
Potential Binding Groups
Phenol
Ether
Alcohol
Amine
HO
O
HO
NMe
© Oxford University Press, 2009.
Structure Activity Relationships
• Mask or remove a functional group
• Test the analogue for activity
• Determines the importance or other wise of a functional group for activity
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NARCOTIC ANALGESICS: MORPHINE AND "PERIPHERALLY MODIFIED" MORPHINE ANALOGS

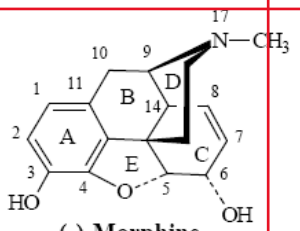
I. Classification of Narcotic Ligands

- Narcotic agonists include natural opium alkaloids (eg, morphine, codeine), semisynthetic analogs (eg, hydromorphone, oxymorphone, oxycodone), and synthetic compounds (eg, meperidine, levorphanol, methadone, sufentanil, alfentanil, fentanyl, remifentanil, and levomethadyl.
- Mixed agonist-antagonist drugs (eg, nalbuphine, pentazocine) have agonist activity at some receptors and antagonist activity at other receptors; also included are the partial agonists (eg, butorphanol, buprenorphine).
- Narcotic antagonists: Narcotic antagonists (eg, naloxone) do not have agonist activity at any of the opioid receptor sites. Antagonists block the opiate receptor, inhibit pharmacological activity of the agonist, and precipitate withdrawal in dependent patients.

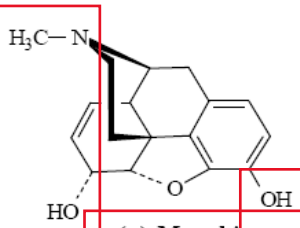
II. Morphine

A. Morphine Structure and Chemistry

The prototypic narcotic analgesic is (-)-morphine, the principal alkaloid obtained from the opium poppy (*Papaver somniferum*). Because of its natural source, morphine and morphine derivatives are referred to as opiates. Narcotic analgesics will be classified on the basis of their structural derivation from morphine.



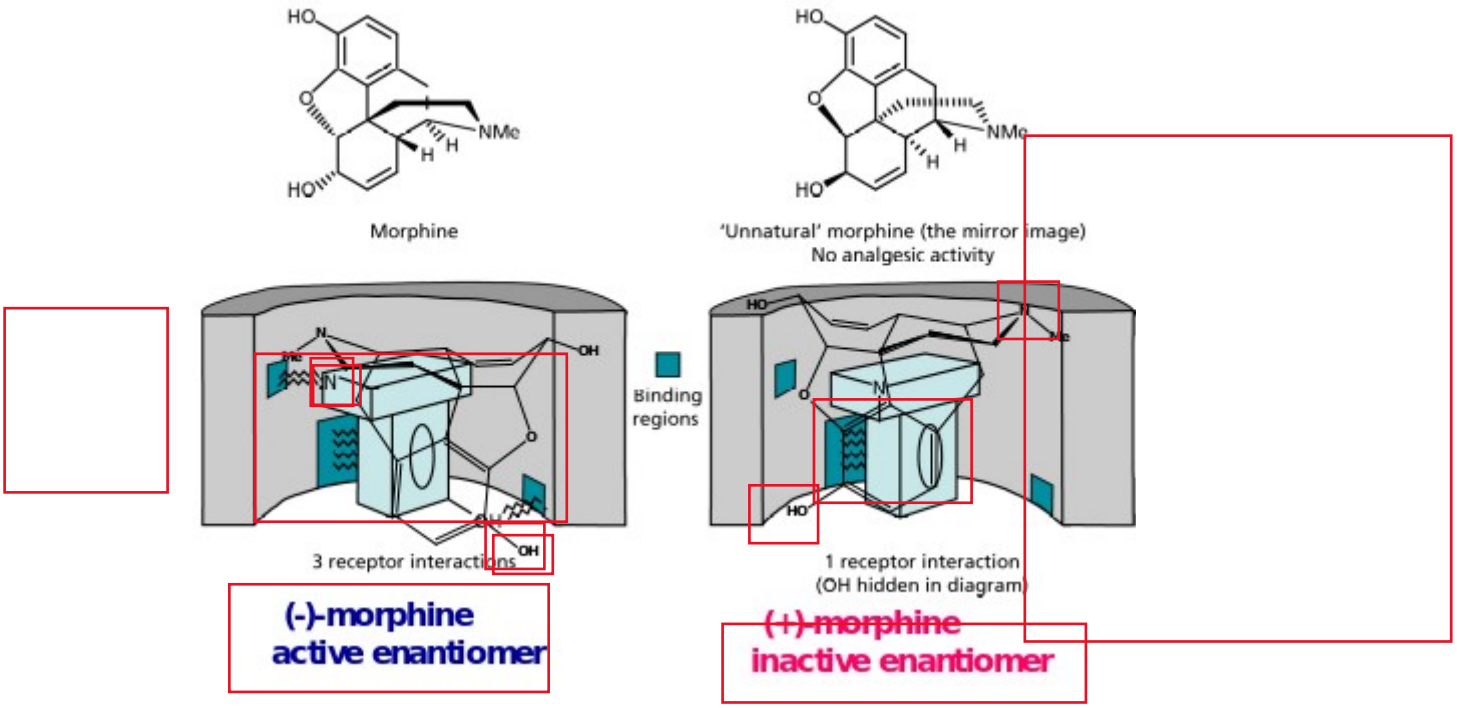
(-)-Morphine

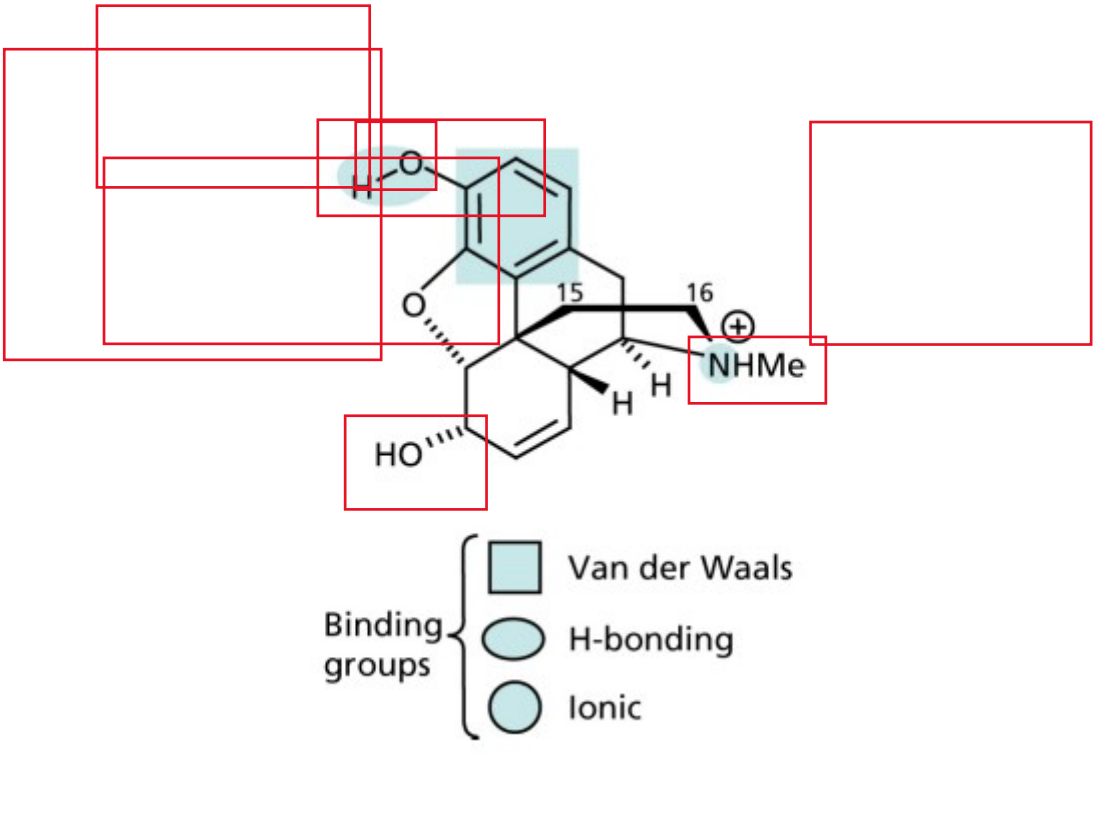


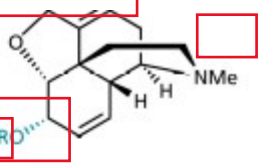
(+)-Morphine

Examination of the morphine molecule reveals the following structural features important to its pharmacological profile:

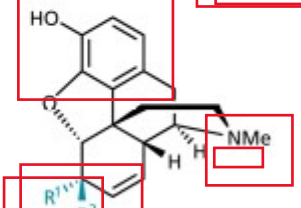
1. A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a dihydrofuran ring (E). Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility (the importance of this will be addressed later).
2. Two hydroxyl functional groups, a C3-phenolic OH (pKa 9.9) and a C6-allylic OH
3. An ether linkage between C4 and C5,
4. Unsaturation between C7 and C8,
5. A basic, 3°-amine function at position 17,
6. 5 centers of chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action. **Only (-)-morphine is active!**


HO
O
NMe
H
H
HO
Morphine
'Unnatural' morphine (the mirror image)
No analgesic activity
Binding regions
3 receptor interactions
1 receptor interaction
(OH hidden in diagram)
(-)-morphine
active enantiomer
(+)-morphine
inactive enantiomer

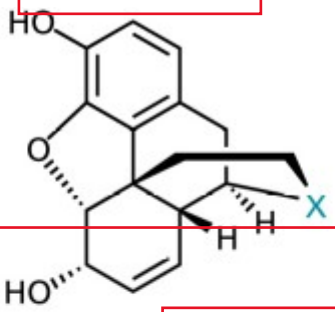

15
16
NHMe
H
H
HO
Binding groups
Van der Waals
H-bonding
Ionic

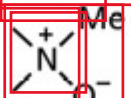
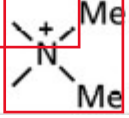


R		Analgesia with respect to morphine
Me	Heterocodeine	5×
Et	6-Ethylmorphine	greater
Acetyl	6-Acetylmorphine	4×

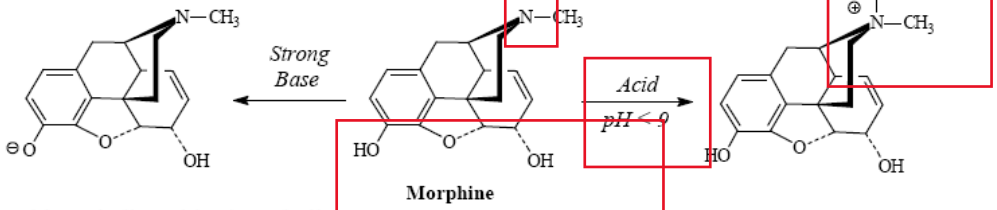


R^1	R^2	Analgesia with respect to morphine
H	OH	Increased
H	H	or
Ketone		similar



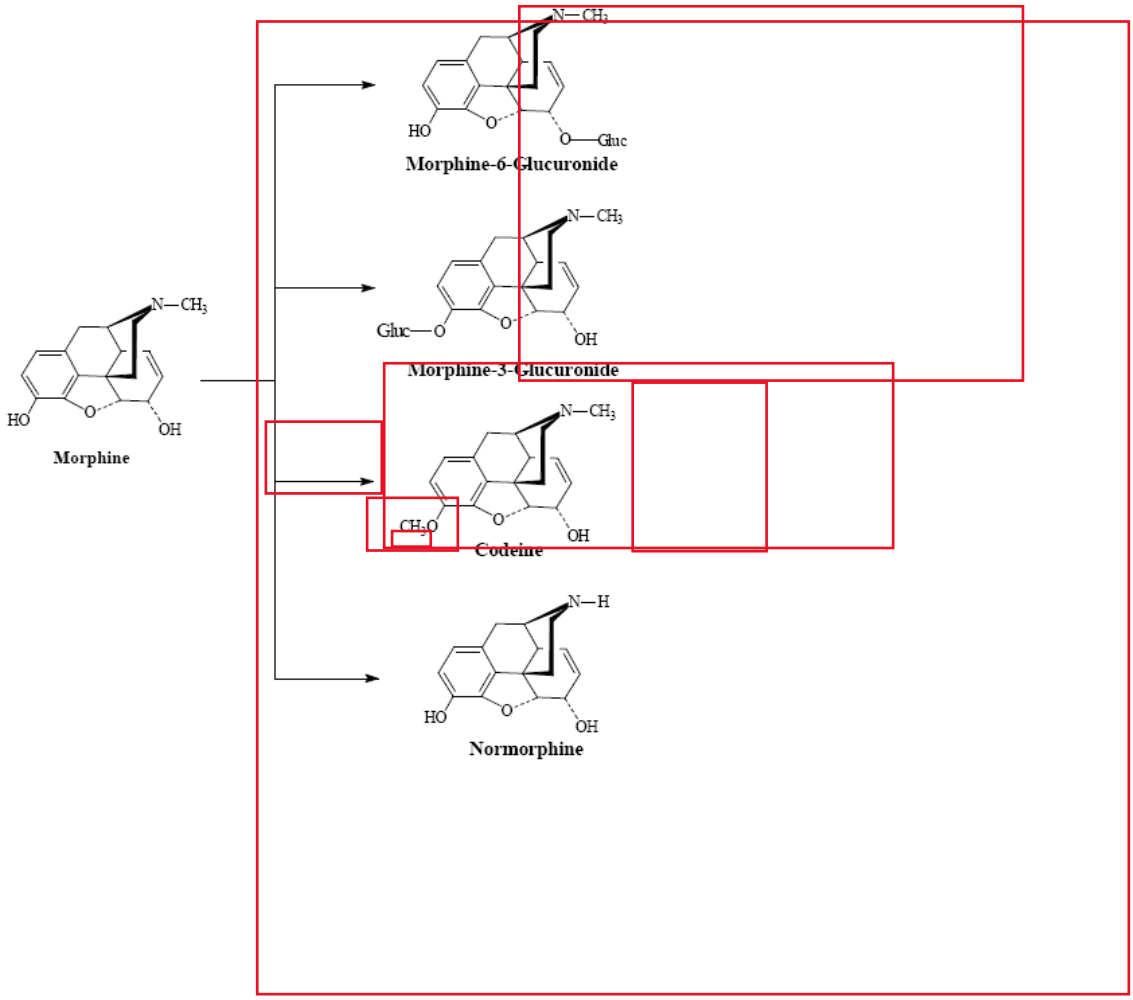
X		Analgesic activity with respect to morphine
NH	Normorphine	25%
	*N*-Oxide	0%
	Quaternary salt	0%

Morphine contains both an acidic phenolic group and a basic tertiary amine functions. However, since the amine functions is significantly more basic than phenol group is acidic, thus, morphine **as well as a majority of narcotic analgesics** are functionally basic compounds both pharmaceutically (dosage forms) and physiologically. Hence, morphine exists as a cation at physiologic pH, and readily forms salts with appropriate acids (commercial products are sulfate and HCl):



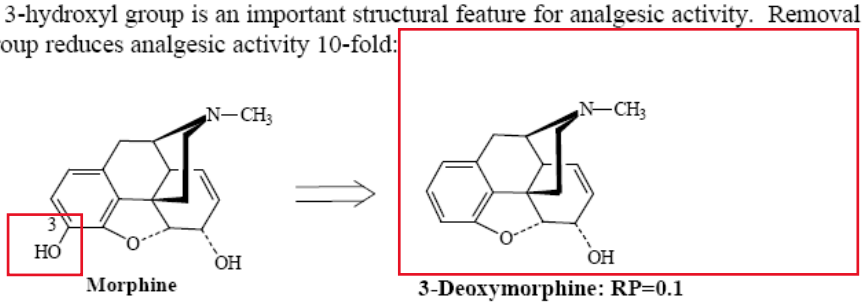
Morphine Biodisposition/Metabolism

- Limited oral bioavailability due to extensive first pass metabolism (see below)
- Lipophilic, but less so than other opioids (i.e. heroin)
- Half-life: 2-3 hrs: Metabolism
- Elimination: Primarily in urine as the glucuronide
- Metabolism: 3- and 6-O-glucuronides, OND and O-methylation to codeine (minor)

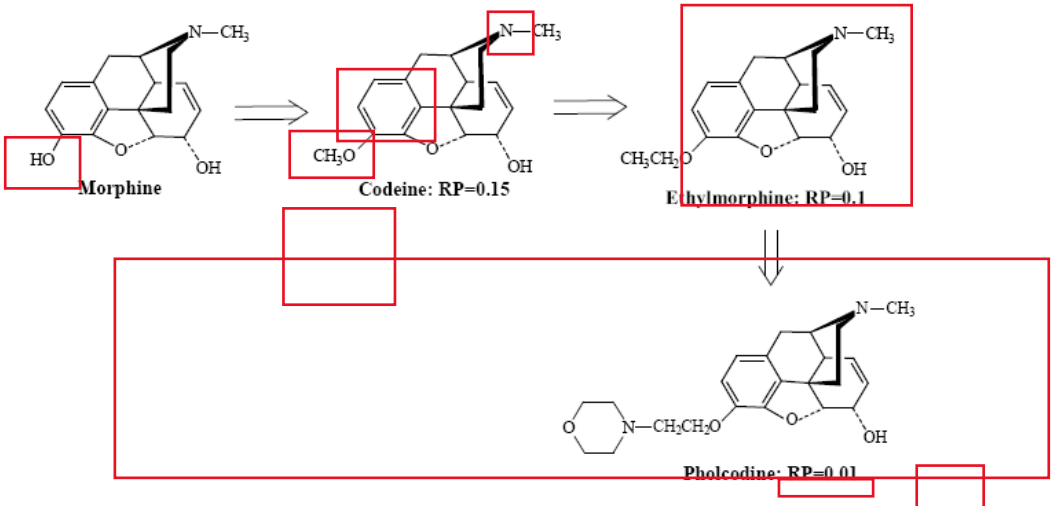


III. "Peripherally Modified Morphines": Ring A Analogues

Ring A and its 3-hydroxyl group is an important structural feature for analgesic activity. Removal of the 3-OH group reduces analgesic activity 10-fold:

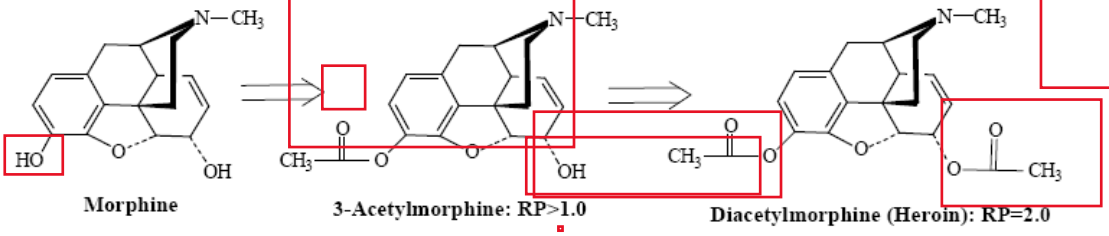


Altering the C-3 OH by etherification as shown by the derivatives below reduces narcotic analgesic activity, the larger the ether group, the lower the analgesic activity. While less active as analgesics, compounds such as codeine possess very useful antitussive activity.



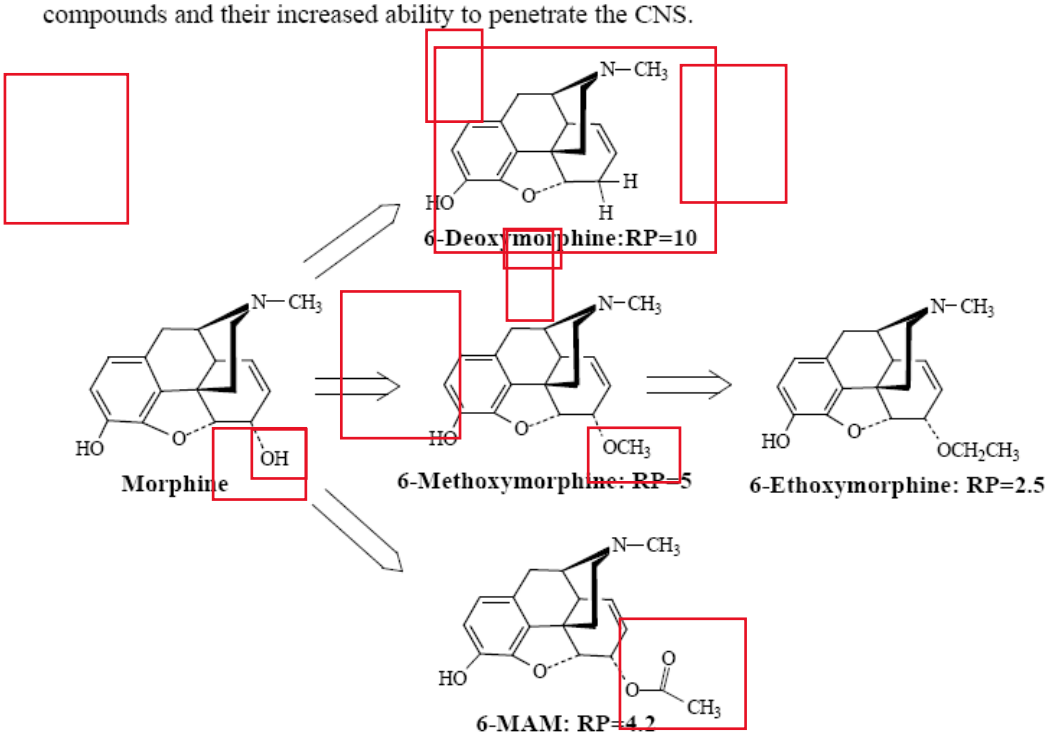
Codeine is available as a sulfate and phosphate salt and also as the free base and as tablets, elixir and solution for injection. The 3-methoxy group protects the 3-position from glucuronide as occurs with morphine. Codeine is used as an analgesic and antitussive. It is metabolized by cytochrome-mediated OOD to morphine (10% of dose), by cytochrome-mediated OND to norcodeine (11% activity of codeine), and conjugation to 6-O-glucuronide. The morphine formed may be further metabolized to by the pathways described above to yield normorphine, conjugates, etc. Some hydromorphone also is reported to form (see structure below)

Derivatization of the C-3 OH by esterification generally only modestly increases activity. Esterification (acetylation) of both the 3- and 6-OH groups yields heroin, a compound which is both more lipophilic and more potent. The primary factor involved in increased analgesic potency is the increased lipophilicity and distribution to the CNS. Heroin is metabolized primarily by hydrolysis of the C-3-0-acetyl moiety to 6-monoacety1morphine (6-MAM). 6-MAM may be further hydrolyzed to morphine which is conjugated with glucuronic acid at C-3-OH (and converted to the other minor morphine metabolites) and eliminated renally.

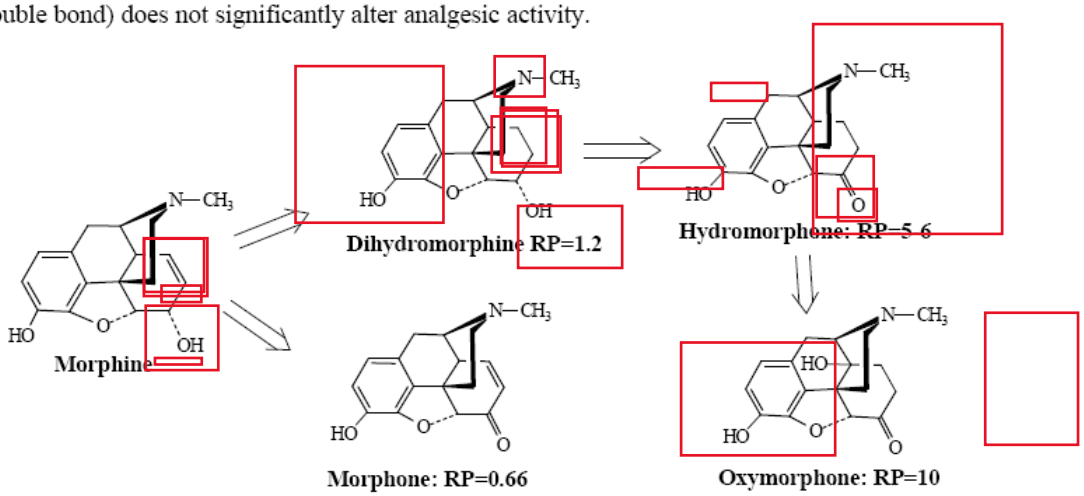


IV. "Peripherally Modified Morphines": Ring C Analogues

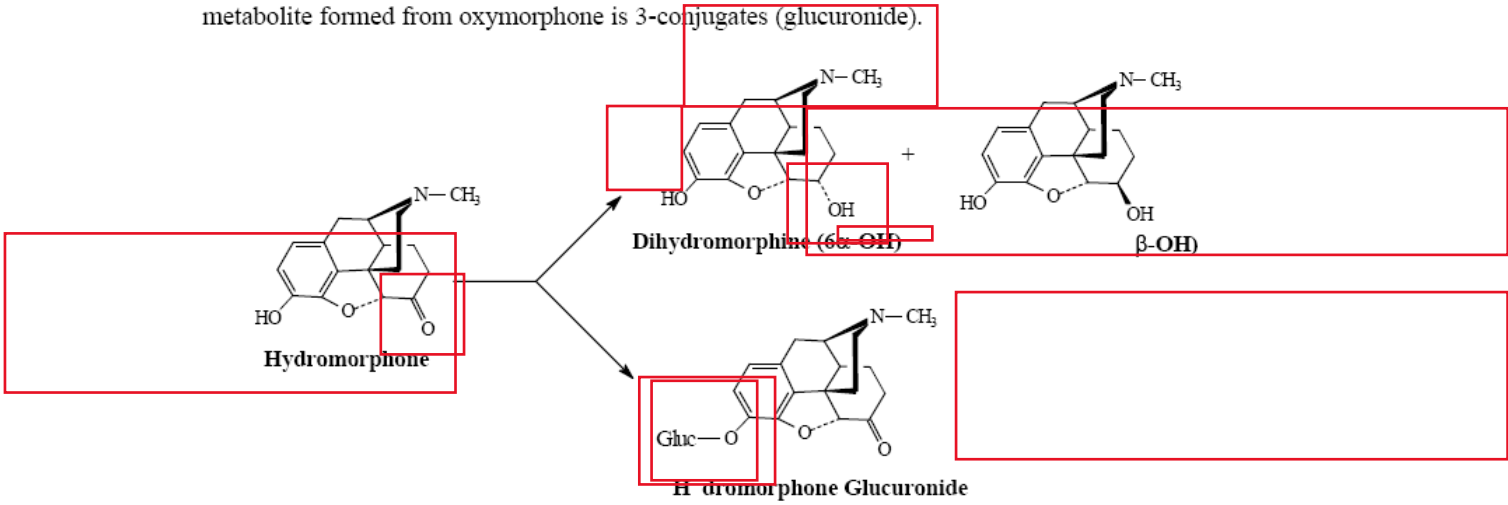
The 6-OH of morphine are not required for analgesic activity as indicated by the relative potencies of the following morphine analogues. Elimination of the 6-OH actually enhances activity. Etherification of this group with relatively small alkyl group also increases activity. Esterification of the 6-OH as in the main hydrolysis metabolite of heroin, 6-MAM, also increases analgesic activity. This increased activity appears to result largely from the enhanced lipophilicity of these compounds and their increased ability to penetrate the CNS.



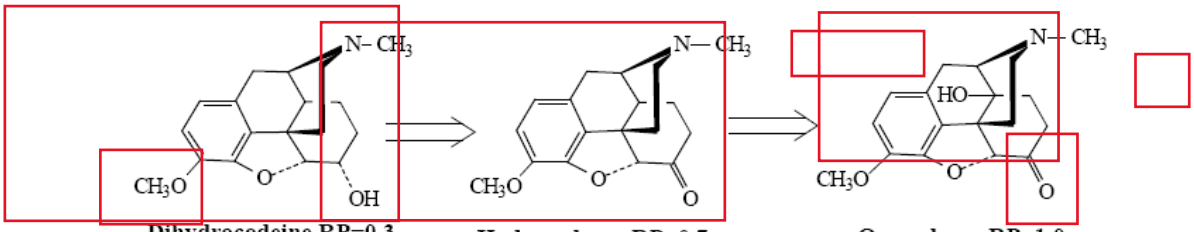
The 7,8-double bond of morphine also is not required for analgesic activity as indicated by the relative analgesic potency of dihydromorphine. Also, oxidation of the 6-OH of dihydromorphine to yield hydromorphone further increases activity. And substitution of a 14-OH group on the hydromorphone structure as in oxymorphone produces a further increase in analgesic activity (RP = 10). Oxidation of the 6-OH of morphine directly as in morphone (without reduction of the 7,8-double bond) does not significantly alter analgesic activity.



Hydromorphone is available as the HCl salt in tablets, liquid, suppository and injectable. It is metabolized to by ketone reduction to the epimeric 6-alcohols (6-OHs) dihydromorphine and dihydroisomorphine. It also undergoes conjugation (glucuronidation) at the 3-OH group. Oxymorphone is available as the HCl salt in a suppository and as an injectable. The primary metabolite formed from oxymorphone is 3-conjugates (glucuronide).



Similar structure activity data is obtained by modification of the codeine structure. Reduction of codeine's 7,8-double bond as in dihydrocodeine increases activity relative to codeine (next page). Oxidation of the 6-OH of dihydrocodeine as in hydrocodone results in a further increase in activity, and 14-OH substitution produces a further increase in analgesic activity.



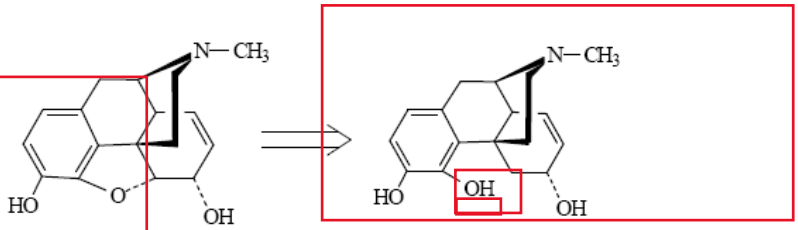
Dihydrocodeine RP=0.3 (Codeine RP=1.15) **Hydrocodone: RP=0.7 (Codeine RP=5)** **Oxycodone: RP=1.0 (Codeine RP=7)**

Hydrocodone is available as the bitartrate salt in tablets and syrups. It has analgesic and antitussive activity. Hydrocodone is metabolized by OOD to hydromorphone (active), by OND to norcodeine (less active) and reduction of the 6-keto group to the two epimeric hydrocodols - 6-beta-hydrocodol and 6-alpha-hydrocodol. The epimeric 6-alcohols can undergo OOD to yield the epimeric hydromorphols - 6-beta-hydromorphol and 6-alpha-hydromorphol. Each of the four 6-OH metabolites have pharmacologic activity equal to or greater than the parent compound, with the exception of 6-alpha-hydrocodol which is one sixth as potent. The structures of these metabolites can be derived from the analogous metabolic reactions described above

Oxycodone is available as the HCl salt in tablets and capsules. It has analgesic and antitussive activity. The primary metabolite formed from oxycodone is 3-conjugates (glucuronide).

V. "Peripherally Modified Morphines": Ring E Analogues

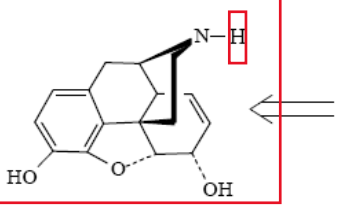
Simple ring-opened analogues of morphine such as the compound below are less active. However, a number of morphine analogues in which this ring and its functionality are completed removed retain high analgesic activity. These analogues are described in the next chapter.



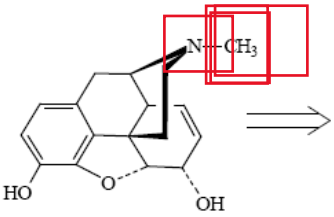
Morphine **RP=0.13**

VI. "Peripherally Modified Morphines": Ring D Analogues and the Tertiary Amine Function

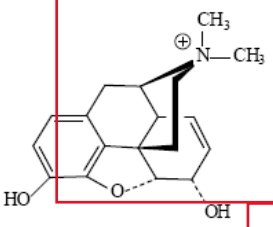
Replacement of morphine's N-methyl group by a hydrogen atom as in normorphine reduces analgesic activity to 1/8th that of morphine. Much of this decrease is due toincreased polarity resulting in reduced BBB translocation to the CNS. The quaternary methiodide analogue of morphine is inactive when administered peripherally (by injection) but equi-active when administered directly into the CNS. The activity of this compound demonstrates the importance of cationic structure of morphine for morphine, and the role of structure in CNS penetration.



Normorphine: RP 0.05

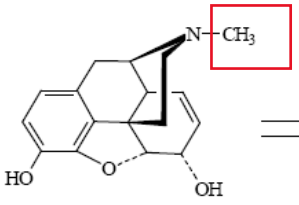


Morphine

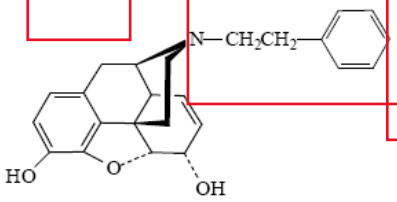


Morphimethine: RP=0.01

Replacement of morphine's N-methyl group with larger alkyl groups reduces activity. However, substitution with aralkyl groups significantly increases analgesic activity as illustrated by N-phenethylnormorphine:

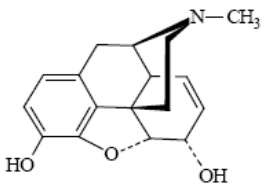


Morphine

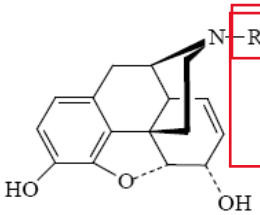


N-Phenethylnormorphine: RP=14

Replacement of morphine's N-methyl group with an allyl group ($-CH_2-CH=CH_2$), a methylcyclopropyl group or a methylcyclobutyl group results in the emergence of opiate receptor **antagonist** activity:



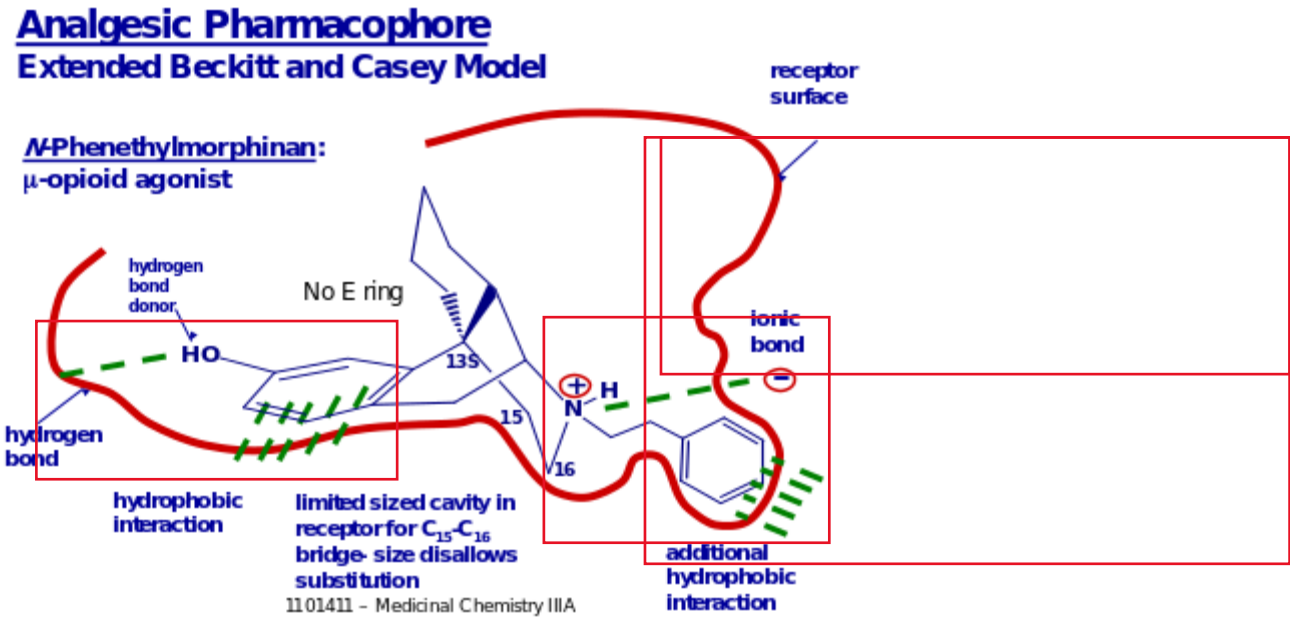
Morphine

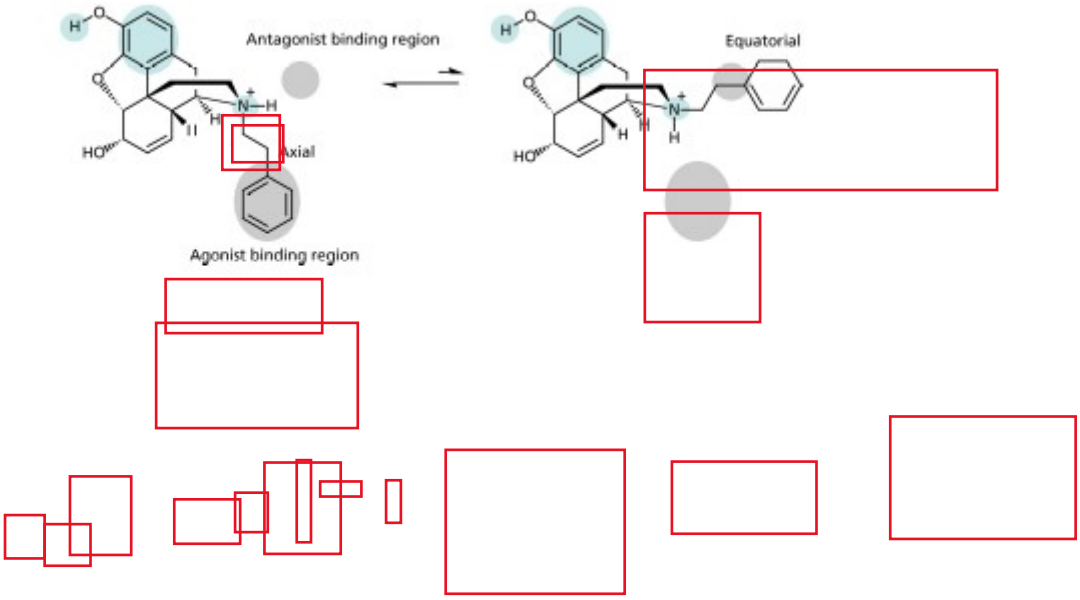


Antagonist activity

R = $-CH_2CH=CH_2$, $-CH_2$-c-C_3H_5, $-CH_2$-c-C_4H_7

Replacement of the potent narcotic agonist oxymorphone's N-methyl group with an allyl group ($-CH_2-CH=CH_2$), a methylcyclopropyl group or a methylcyclobutyl group also results in the emergence of opiate receptor **antagonist** activity (see structures on the next page). Three of these compounds - naloxone HC1 (Narcan) naltrexone HCl (Trexan) and nalmefene (Revex) - are pure opiate antagonists (at mu, kappa and delta receptors) and are used for the reversal of the narcotic/respiratory depression induced by opiate agonists, as well as psychotomimetic actions. These compounds are also used as adjuncts to the maintenance of an opiate-free state in detoxified, formerly opiate-dependent patients.


Analgesic Pharmacophore
Extended Beckitt and Casey Model
receptor surface
N-Phenethylmorphinan:
μ-opioid agonist
hydrogen bond donor
No E ring
HO
13S
15
16
N
H
ionic bond
hydrogen bond
hydrophobic interaction
limited sized cavity in receptor for C15-C16 bridge- size disallows substitution
additional hydrophobic interaction
1101411 – Medicinal Chemistry IIIA

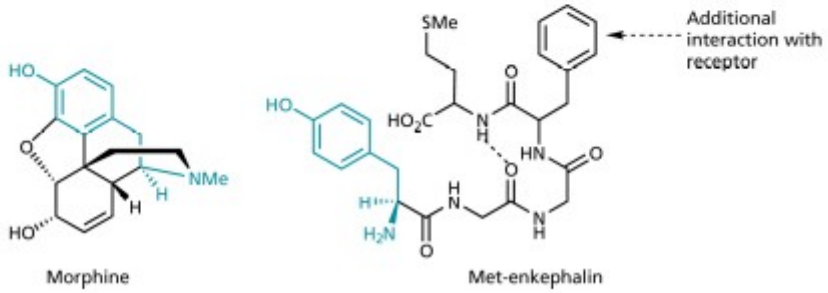


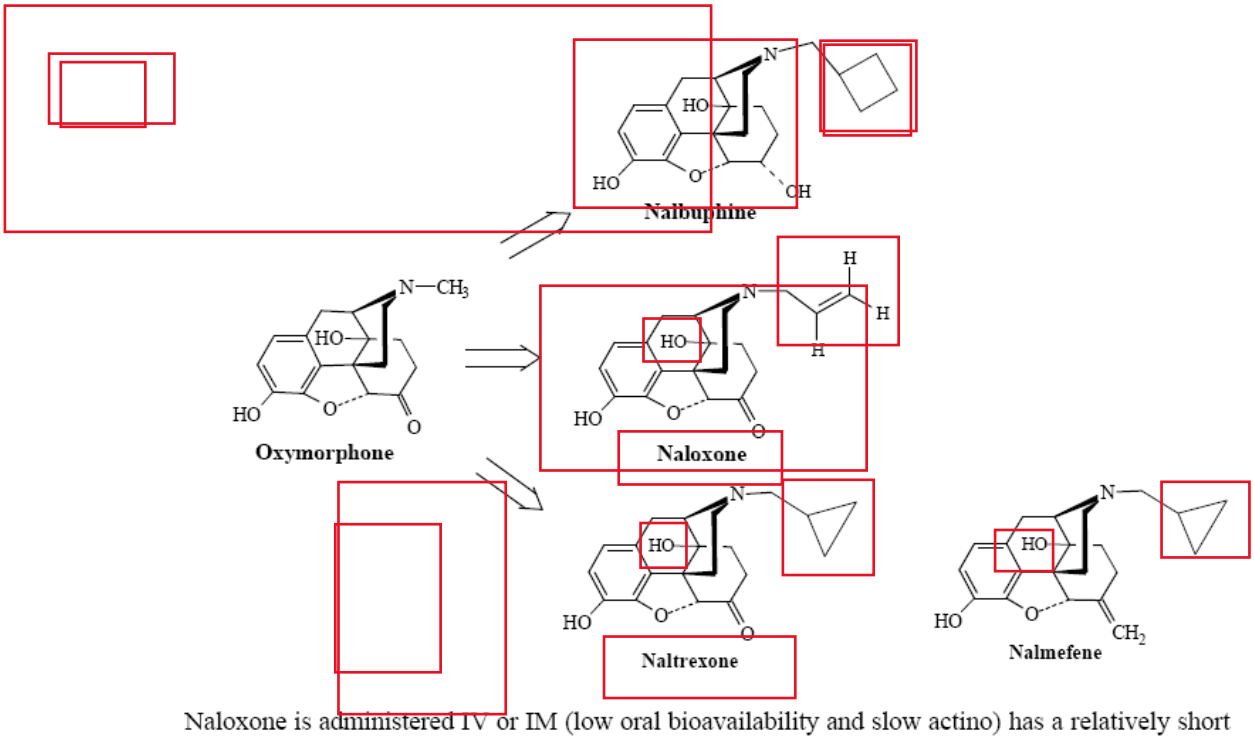
H-Tyr-Gly-Gly-Phe-Met-OH
Met-enkephalin

H-Tyr-Gly-Gly-Phe-Leu-OH
Leu-enkephalin

Proenkephalin
Prodynorphin
Pro-opiomelanocortin

→ Endorphins + enkephalins

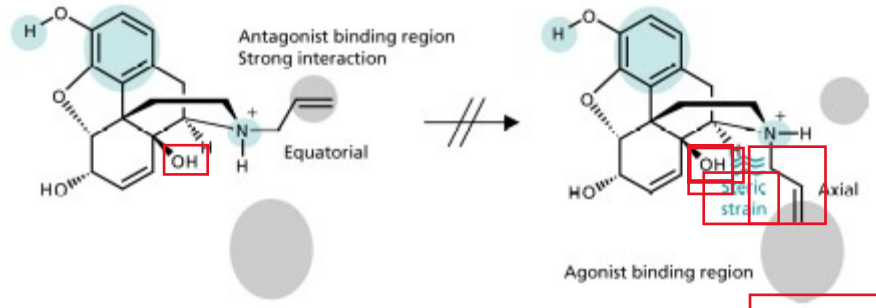


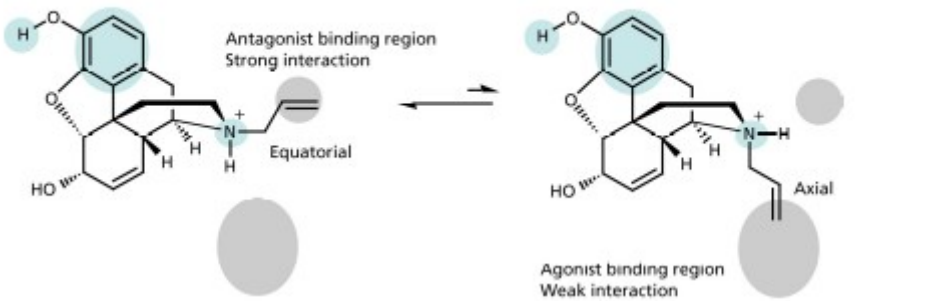


Naloxone is administered IV or IM (low oral bioavailability and slow actino) has a relatively short half-life (1 hour). Naltrexone is used orally and has a substantially longer half-life (10 hours) and duration (24-48 hours) of action. Naltrexone is adminsitered by injection. It also has a longer half-life (10 hours) and duration than naloxone.

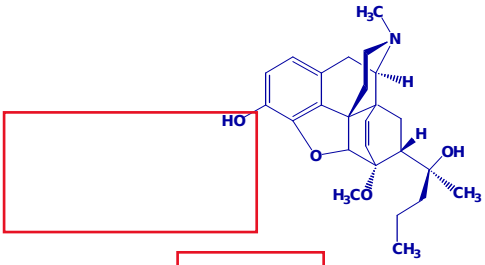
Nalbuphine HC1 (Nubain) is a mixed opiate agonist/antagonist. It functions as a potent antagonist at μ-receptors, and an agonist equipotent with morphine at κ_1 and κ_3 receptors. The antagonist actions of the drug accounts for a ceiling effect on respiratory depression and a low abuse potential. Nalbuphine is available as a solution for IM injection. It has the same time of onset and duration of action.

The metabolism of the narcotic antgaonists/mixed agonists or antagonistst has not been extensively studied. Nalmefene is known to undergo 3-O-glucuronidation and, to a lesser extent, N-dealkylation. The other compounds are presumed to be metabolized similarly.

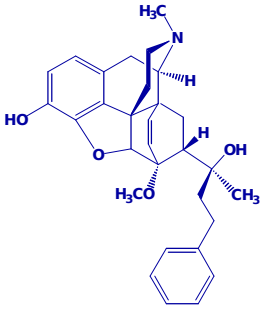

Antagonist binding region
Strong interaction
Equatorial
Axial
Agonist binding region


Antagonist binding region
Strong interaction
Equatorial
Axial
Agonist binding region
Weak interaction

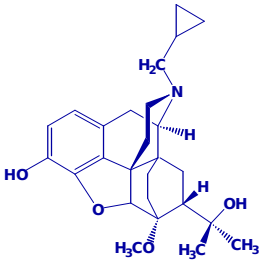
Structures of Selected Oripavines



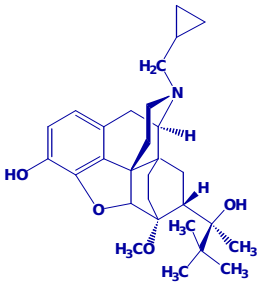
etorphine, Immobilon, agonist
10,000x activity of morphine



"phenyletorphine", PET, agonist
activity > etorphine



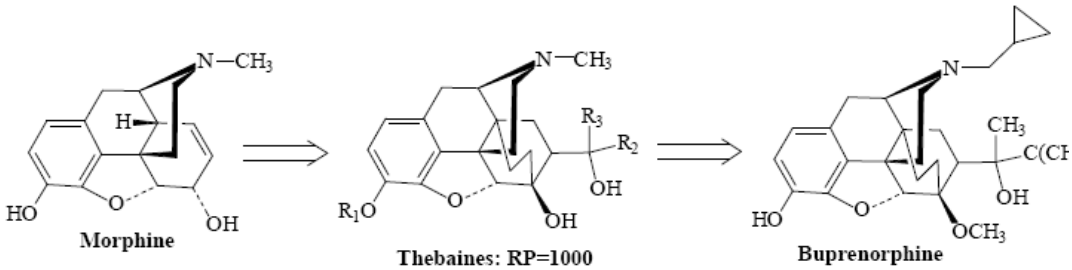
diprenorphine, Revivon, antagonist
100x activity of nalorphine



buprenorphine, agonist/antagonist
agonist, 100x activity of morphine
antagonist, 4x activity of nalorphine

VII. "Peripherally Modified Morphines": The Thebaines

Annelation – adding a sixth ring across carbons 6 and 14 of the C ring of morphine - yiel thebaine compounds such as etorphine which are extremely potent analgesics. These compoun as typically used to immobilize large animals (elephants).



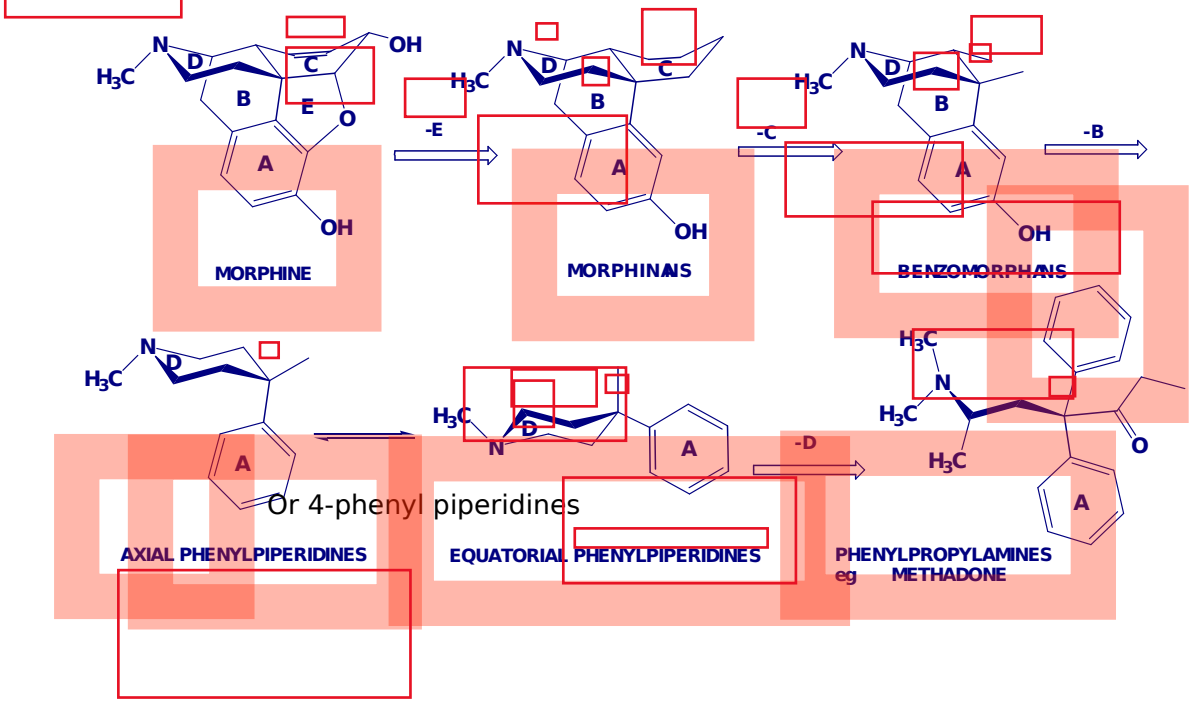
Replacement of the N-methyl group of the thebaines with a methylcyclopropyl group yiel compounds with mixed agonist/antagonist or partial agonist activity. For example, buprenorphi HC1 (Buprenex) is a partial opiate agonist at μ-receptors and an antagonist at κ_1 receptors. A an agonist it is 25-50 times more potent than morphine and slightly longer acting. It is availab for IM and sublingual administration and has a half-life of about 5 hours. The metabolic pathwa for buprenorphine are not known. It's respiratory depressant activity reaches a ceiling. It h moderate abuse potential. Because of its high affinity and slow dissociation from opia receptors, larger doses of antagonists such as naloxone are required to produce reversal.

Table of Receptor Activities for the Narcotic Analgesics

Opioid	μ	δ	κ	σ
Leu-enkephalin	+	+++		
Met-enkephalin	++	+++		
Morphine	+++	+	++	
Codeine	+	+	+	
Etorphine	+++	+++	+++	
Fentanyl	+++	+		
Sufentanil	+++	+		
Penatzocine	-	+	(++)	+
Nalbuphine	-	+	(++)	+
Nalorphine	--	(++)	(++)	+
Buprenorphine	(+++)			
Antagonists				
Naloxone	---	--	--	
Naltrexone	---	--	--	

+ agonist, - antagonist, (+) partial agonist

Ring Removal - Nomenclature

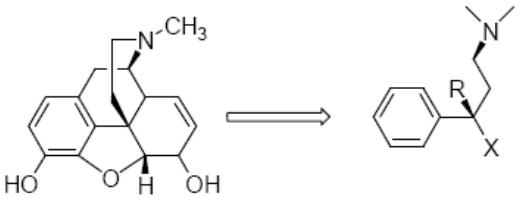


Or 4-phenyl piperidines

NARCOTIC ANALGESICS: "NUCLEAR MODIFIED" MORPHINE

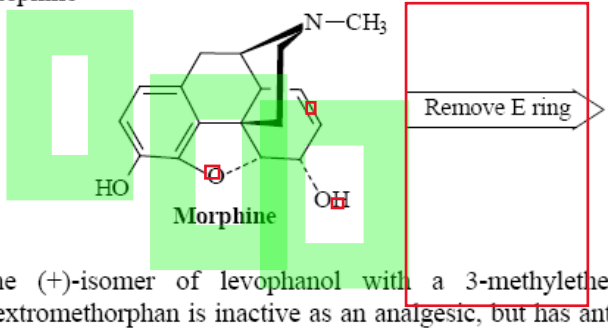
I. Introduction: The "Synthetic Narcotic Analgesics"

More extensive structural modification of morphine has been carried out in an attempt to achieve more favorable separation of therapeutic (analgesia, antitussive) and adverse (respiratory depression, sedation, physical dependence) reactions. Continued SAR studies of nuclear modified opiates suggested that a minimum " structural" pattern (analgesiophore) exists in the relatively complex morphine structure that is primarily responsible for narcotic analgesia produced by this agent. The analgesiophore consists of an aromatic ring linked to a quaternary carbon which, in turn, is connected via a two carbon atom chain to a tertiary, basic amine. These studies led to the design and development of narcotic analgesics of simpler structure which are outlined below.



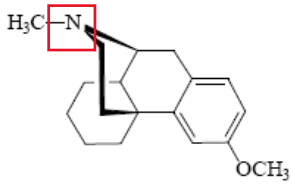
II. Morphinans

Morphinans are structurally derived from morphine by removal of the ether oxygen (ring E) and therefore elimination of the E-ring. The (-)-morphinan analogue derived from such a modification is levorphanol (Levo-Dromoran) which is a mu and kappa-3 receptor agonist. It is approximately 5-8 times more potent than morphine both as an analgesic and respiratory depressant, but produces less nausea and vomiting. Levophanol is more lipophilic than morphine and has a greater oral/parenteral potency ratio (2:1). It is available as a bitartrate salt which is administered orally and by injection (IM and SC) and has a duration of 3-6 hrs. It is cleared primarily by 3-O-glucuronidation similar to morphine



Morphine **Levorphanol**

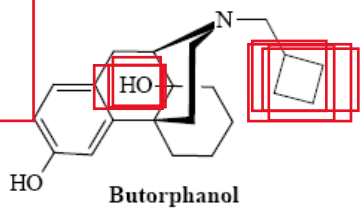
The (+)-isomer of levophanol with a 3-methylether group is dextromethorphan. Dextromethorphan is inactive as an analgesic, but has antitussive potency equal to that of codeine.



Dextromethorphan

1

Replacement of the N-methyl moiety in the morphinan series with an N-allyl or N-cycloalkyl groups results in partial agonist activity. Butorphanol tartrate (Stadol) is an agonist at σ and κ-opiate receptors and a partial agonist/antagonist at μ-receptors. As an analgesic (agonist) it is 5-times more potent as an analgesic than morphine with a similar onset and duration of action, a ceiling effect on the degree of respiratory depression occurs after about twice the usual therapeutic dose, has low abuse liability. As a μ-antagonist this compound is about 6 times less potent than naloxone:

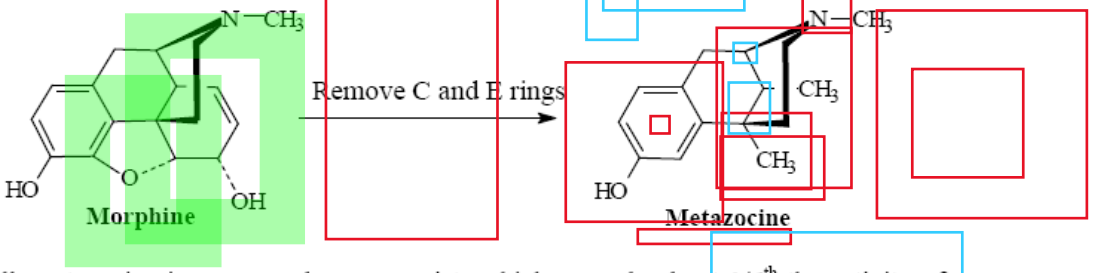


Butorphanol

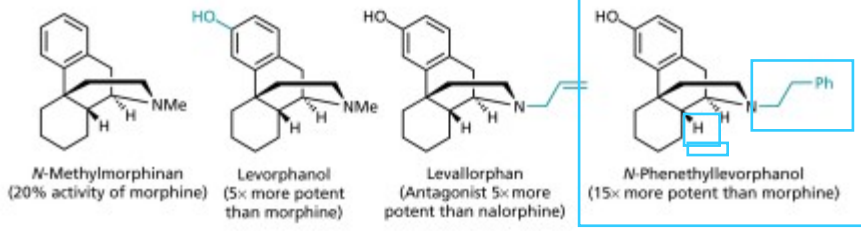
Butorphanol is available as the tartrate salt with is administered IM, SC and IV. It is metabolized by hydroxylation.

III. 5,9-Dimethylbenzomorphans

Benzomorphans such as metazocine shown below are structurally derived from morphine via cleavage of both ring C and E. Removal of these rings yields a benzomorphan ring system that has conformational flexibility (unlike the morphines and morphinans), thus different ring conformational extremes may exist. Also, the presence of methyl substituents at positions 5 and 9 in these compounds produces sites of asymmetry. Thus the benzomorphans can exist in different stereoisomeric and conformational forms (see next page). As noted earlier, the opiate receptors are capable of stereoselective ligand binding. Thus it is not surprising that different stereoisomeric forms of the benzomorphans differing analgesic potency. In the case of the metazocine, the trans-5,9-diCH_3 stereoisomers (also termed beta isomers) are significantly more active as analgesics than the cis- (alpha) geometric isomers.



Overall, metazocine isomers are kappa agonists which are only about $1/6^{th}$ the activity of morphine. Metazocine is available as HCl and tartrate salts which are orally active. The oral/parenteral potency ratio is 2:1. These compounds are metabolized 3-O-glucuronidation and hydroxylation of the side chain methyl groups.

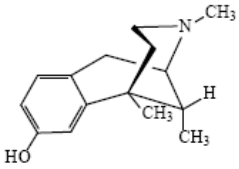


N-Methylmorphinan (20% activity of morphine)

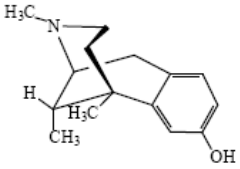
Levorphanol (5× more potent than morphine)

Levallorphan (Antagonist 5× more potent than nalorphine)

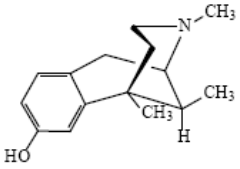
N-Phenethyllevorphanol (15× more potent than morphine)



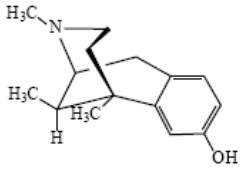
(-)-Alpha-isomer (cis)



(+)-Alpha-isomer (cis)



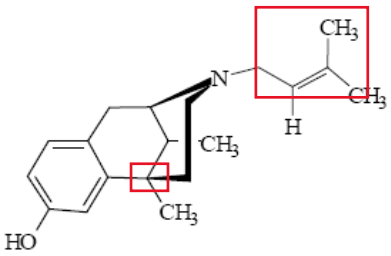
(-)-Beta-isomer (trans)



(+)-Beta-isomer (trans)

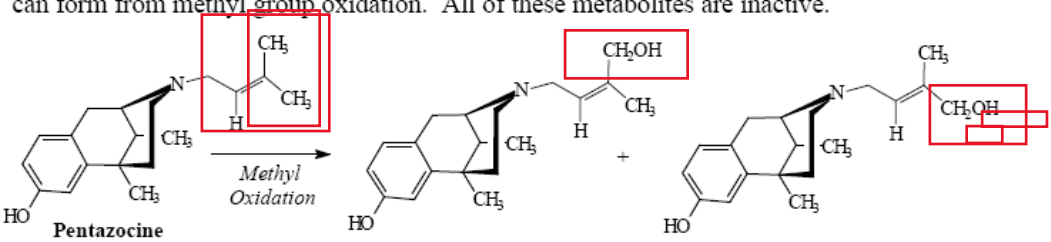
More active isomers

Replacement of the N-methyl of metazocine with an N-allyl group yields pentazocine (Talwin). This compound is a relatively strong opiate agonist at kappa receptors and weak agonist/antagonist at mu receptors. It is most effective vs. moderate pain but tolerance and abuse potential do exist.



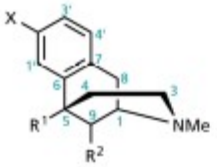
Pentazocine

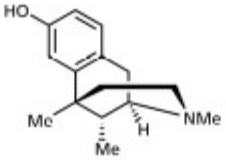
Pentazocine is available for oral administration and injectables (IM, SC). It's oral bioavilability is relatively due due to extensive first pass metabolism by 3-O-glucuronidadtion and terminal methyl group oxidation; two different geometric isomers can form from methyl group oxidation. All of these metabolites are inactive.



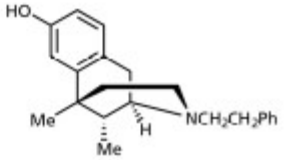
Pentazocine

Methyl Oxidation Isomers

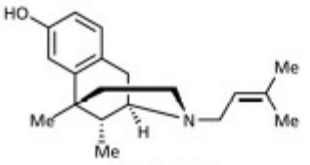




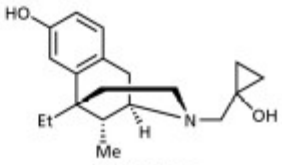
Metazocine
(same potency as morphine)



Phenazocine
(4× more potent than morphine)



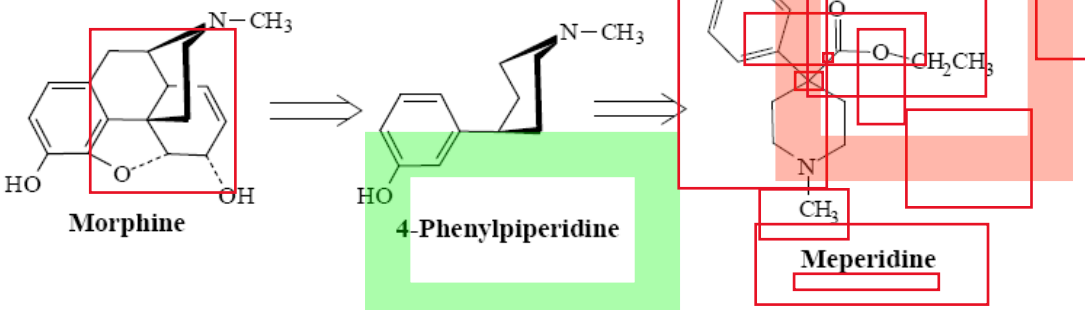
Pentazocine
(33% activity of morphine, short duration,
low addiction liability)



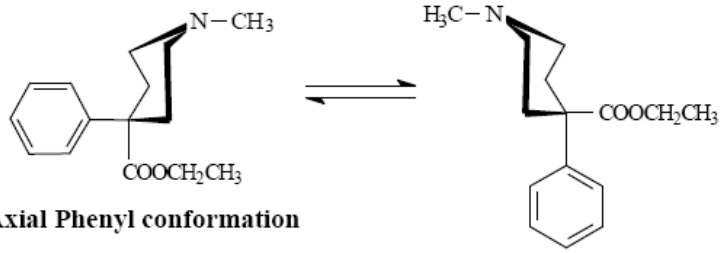
Bremazocine

IV. 4-Phenylpiperidines (4-PP)

The 4-phenylpiperidines can be regarded as analogues of morphine in which rings B, C and E have been removed as illustrated by the figure below and the example of meperidine:



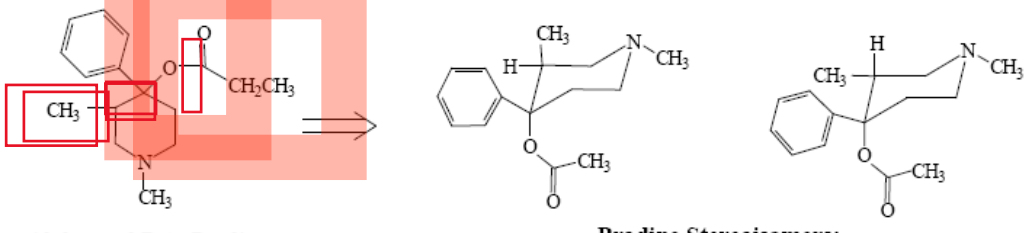
Meperidine (Demerol) is the only 4-PP currently marketed in the U.S. It is an achiral analgesic that can exist in two different conformation extremes resulting from piperidine ring conformation inversion. In these conformations, the relative positions of the 4-substituents interconverts from axial to equatorial. It is believed that the conformation with the 4-phenyl group in the axial orientation in most stable and may be bound by opiate receptors:



Axial Phenyl conformation

Equatorial Phenyl conformation

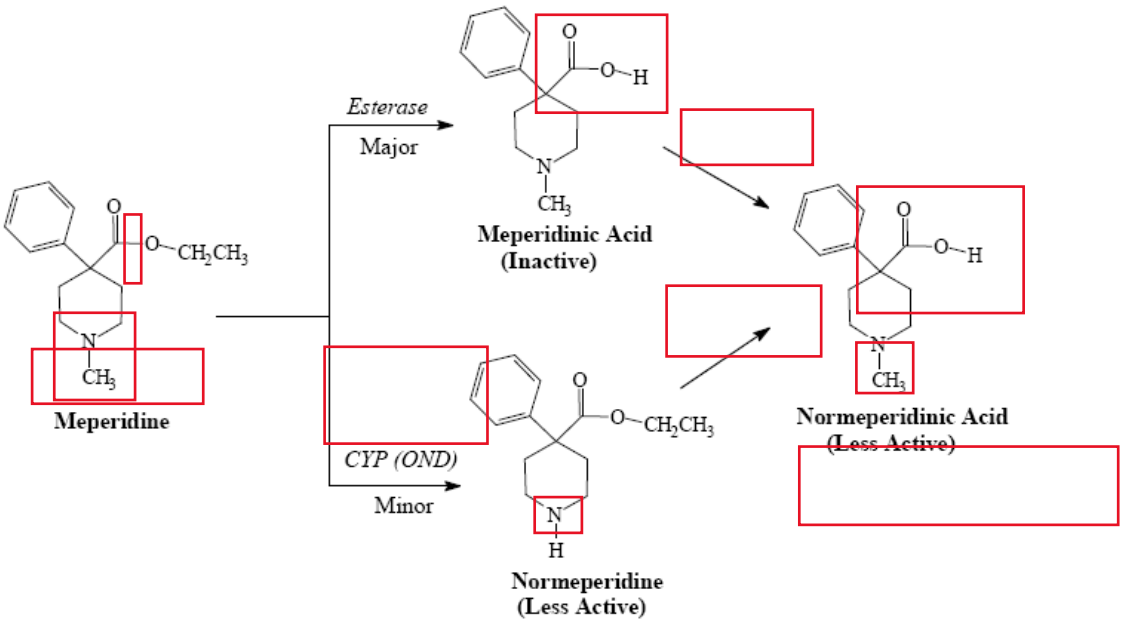
Another class of 4-phenylpiperidines are the "prodines" these are analogues of meperidine in which the ester functionality has been "reversed" (not really singificant here) and a methyl substitutent added to the 3-position of the piperidine ring (significant). The additional methyl group creates chirality at both positions 3 and 4-stereochemical and thus provides an interesting experimental compound to study the relationship between opioid stereochemistry and opiate receptor binding:



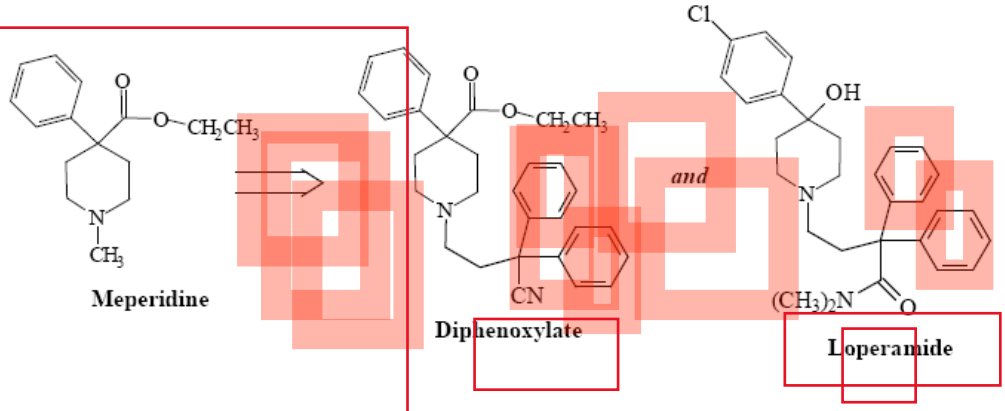
Alpha- and Beta-Prodines

Prodine Stereoisomers:

Meperidine is a mu agonist but is 5-10 times less potent than morphine. It is no antitussive activity. Meperidine is available as the HCl salt for oral administration (tablets, syrup) and a solution for injection (IM). Meperidine has relatively high oral bioavailability (o/p ratio of 3:1) producing, at equi-effective doses, the same degree of analgesia, sedation and respiratory depression. Meperidine has a relatively short duration of action due to efficient inactivation by ester hydrolysis to meperidinic acid. A fraction of the dose is also metabolized by oxidative-N-dealkylation, leading to the formation of normeperidine which has been implicated in the CNS toxicity of meperidine. Meperidinic acid and nomeperdine form a common normeperidinic acid which is conjugated and eliminated:

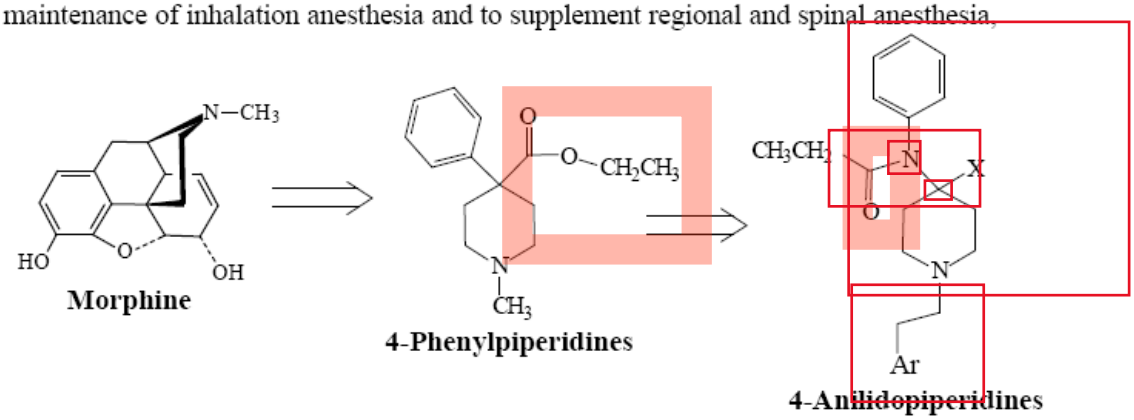


Several merpidine-type analogues, or meperidine/methadone hybrid analogues including diphenoxylate (Lomotil) and Loperamide (Imodium) have been developed as antidiarrheal agents. These compounds have minimal analgesic activity, but retain the GI motility-inhibiting actions of the classic morphine-type drugs.



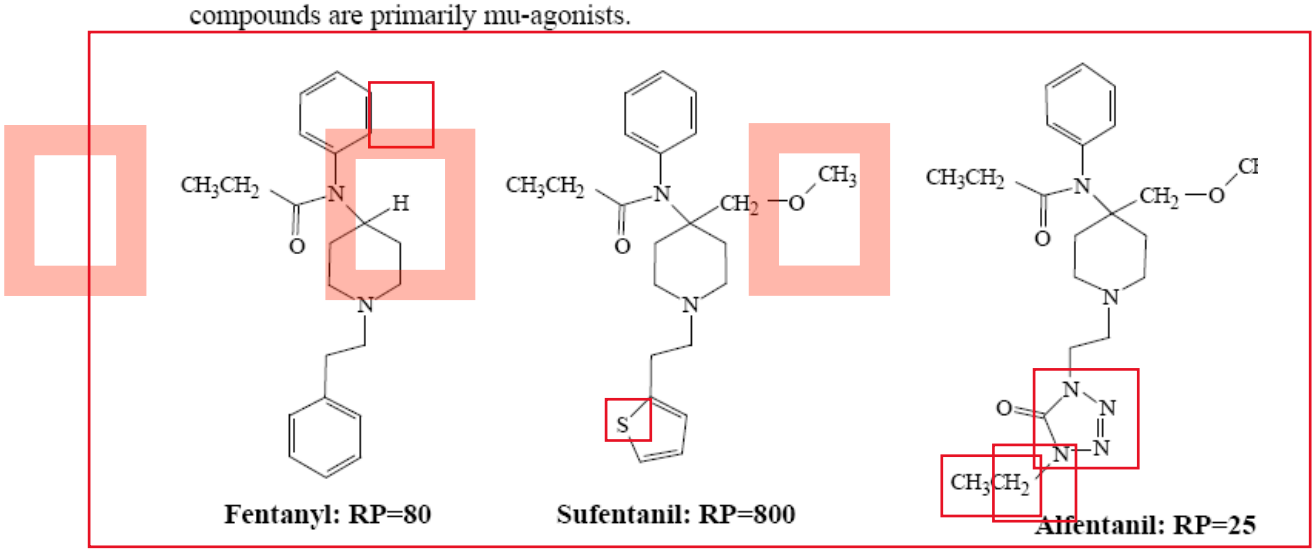
V. 4-Anilidopiperidine (4-AP) Derivatives

The 4-anilidopiperidines can be regarded as derivatives of the 4-phenylpiperidines in which a nitrogen atom has been inserted between the piperidine ring and the aromatic ring. Generally 4-anilidopiperidines are extremely potent narcotic analgesics (200 to 500 X morphine) with significant sedative properties. Thus they are used to aid the induction and maintenance of inhalation anesthesia and to supplement regional and spinal anesthesia.



Morphine **4-Phenylpiperidines** **4-Anilidopiperidines**

The commercially available 4-anilidopiperidines inlcude the parent or prototype, fentanyl (Sublimaze) and sufentanil (Sufenta), alfentanil (Alfenta) and remifentanil (discussed later). These compounds differ only in the nature of the piperdine N-arethylaryl substituent, and the nature of the "other" substituent at the 4-position. All of these compounds are primarily mu-agonists.



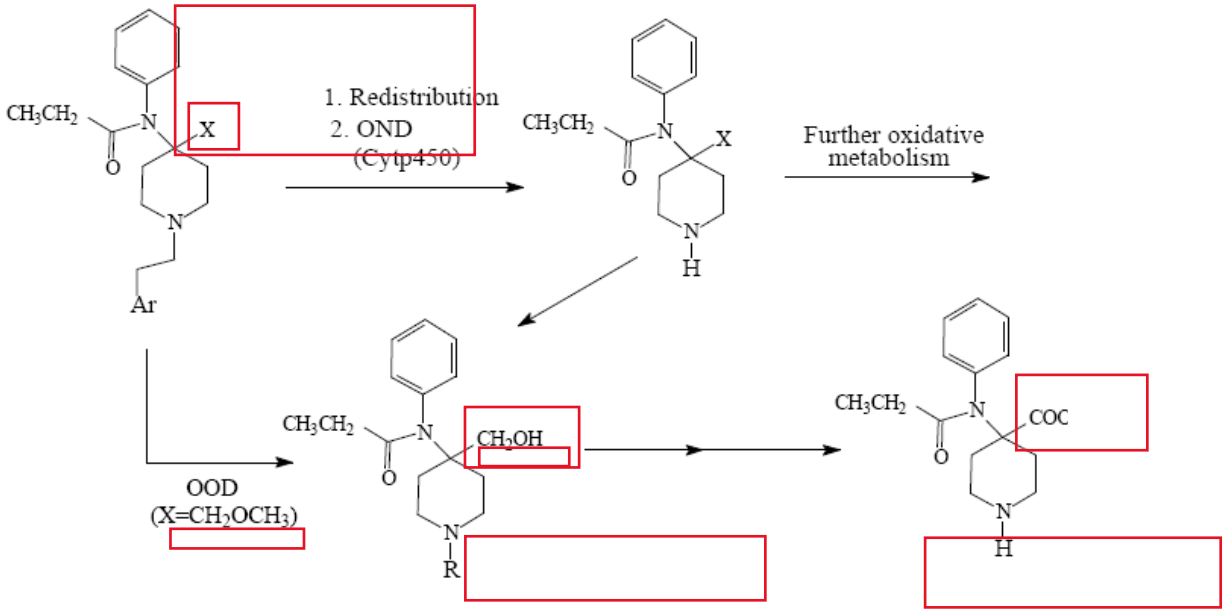
Fentanyl: RP=80 **Sufentanil: RP=800** **Alfentanil: RP=25**

- Fentanyl is 25-80 times more potent than morphine with a shorter duration of action. Fentanyl is avilable as the citrate salt for injection (IM or IV) and transdermal patches. It is combined with droperidol (Innovar) and used to induce anesthesia.
- Sufentanil (Sufenta) is about 7-times more potent than fentanyl (about 800 times more potent than morphine) and has a slightly more rapid onset of action. It is available as

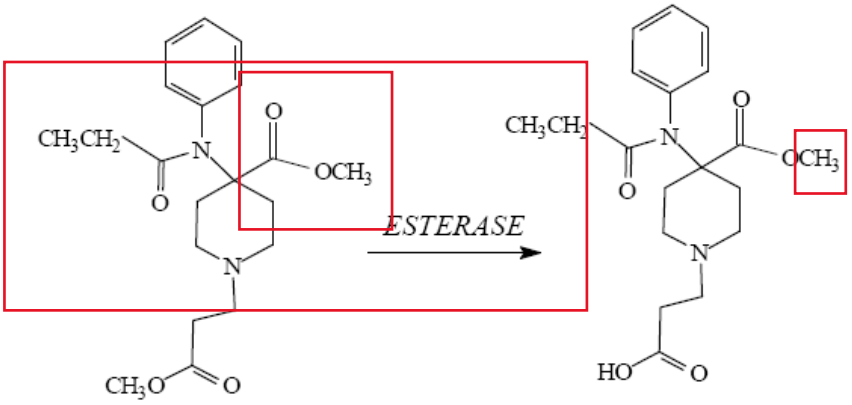
the citrate salt as a solution for injection (IV) and used to induce anesthesia and for postoperative analgesia.

- Alfentanil (Alfenta) is about as potent as fentanyl and has a shorter duration of action. It is avilable as the HCl salt for IV injection) and used to induce anesthesia and for postoperative analgesia.

Due to a similar (isosteric) N-arylethyl fragment present in all of the 4-anilidopiperidines, these compound are metabolized by a common pathway involving cytochrome-mediated N-dealkylation (see figure below). In fact, since alfentanil and sufentanil differ only in the nature of the aryl group in the N-arylethyl fragment, these two 4-anilidopiperidines yield the SAME OND metabolite. The OND metabolites formed from the 4-anilidopiperidines are inactive as analgesics. Alfentanil and sufentanil also contain a 4-methoxymethyl substituent which undergoes cytochrome-mediated oxidative O-demethylation (see below). The alcohol products formed from this reaction retain analgesic activity, but are oxidized to the corresponding acids which are inactive.



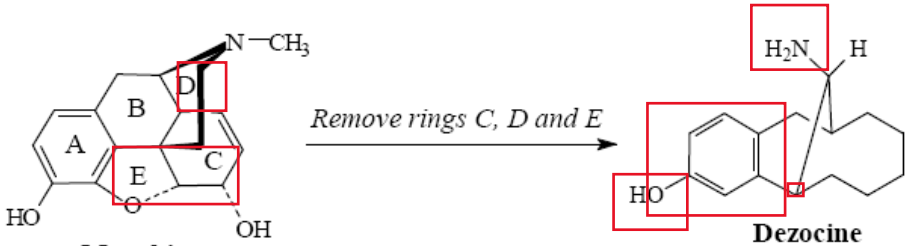
Remifentanil is a 4-anilidopiperidine designed as a soft drug. It is similar to the other members of this series in its pharmacologic profile and is 20-50 times more potent than alfentanil. Remifentanil differs from the other 4-anilidopiperidines in that it is designed as a "soft drug" – a compound that is designed to be metabolized rapidly so it has a relatively short duration of action:



Remifentanil: RP >500 **Remifentanil Acid (Inactive)**

VI. Aminotetralines: Dezocine

Dezocine (Dalgan), a synthetic bridged aminotetralin is a structurally-novel partial (mixed) opioid agonist/antagonist. This is the only primary amine compound to display opioid activity! Dezocine's profile of opiate receptor subtype affinity is similar to that of morphine with partial agonist activity at μ-receptors (RP=1). The incremental analgesia observed with successive doses of dezocine in addition to somnolence elicited by the drug suggest activity at opiate κ-receptors. Unlike pentazocine, butorphanol and nalbuphine, dezocine does not possess high affinity for σreceptors. The compound is 8.6 times more potent than pentazocine as a respiratory depressant, however a ceiling respiratory effect occurs for this agent at 0.30 mg/kg.

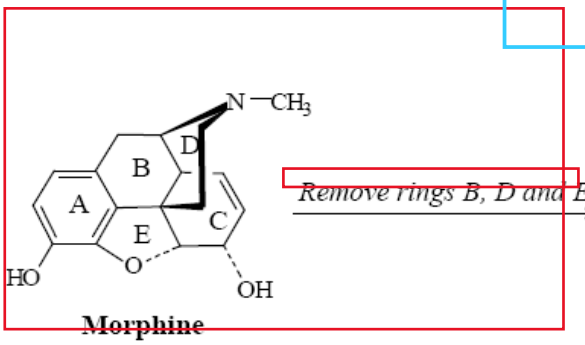


Morphine **Dezocine**

Dezocine is available as a a solution for IM, SC or IV injection. It is cleared by glucuronidation and reductive metabolism (?).

VII. Arylcyclohexanolamines: Tramadol

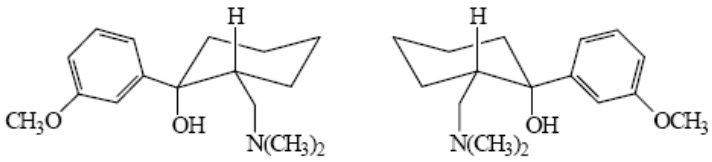
Analogue of codeine in which rings B, D and E have been removed. This structure contains two chiral centers (positions 3 and 4 of the cyclohexane ring), thus there are four potential stereoisomers – enantiomeric cis and trans isomers (see below). The racemic cis isomers are active and make up the commercial product.



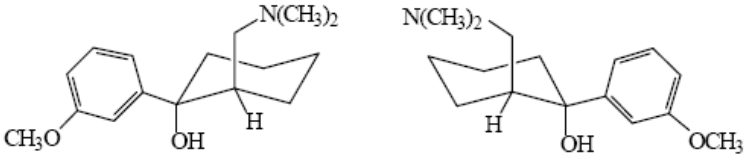
Morphine **Tramadol**

Tramadol (Ultram) is a mu agonist that is substantially less potent than morphine as an analgesic (more than 100 fold less active). This product also has peripheral analgesic actions. Tramadol has high oral activity and is metabolized by cytochrome-mediated oxidative-O-demethylation to the corresponding 3-phenol which is more active than the parent drug. The phenol is glucuronidated and eliminated. A fraction of the tramadol dose is also metabolized by cytochrome-mediated oxidative-N-demethylation to less active metabolites.

TRAMADOL STEREOISOMERS



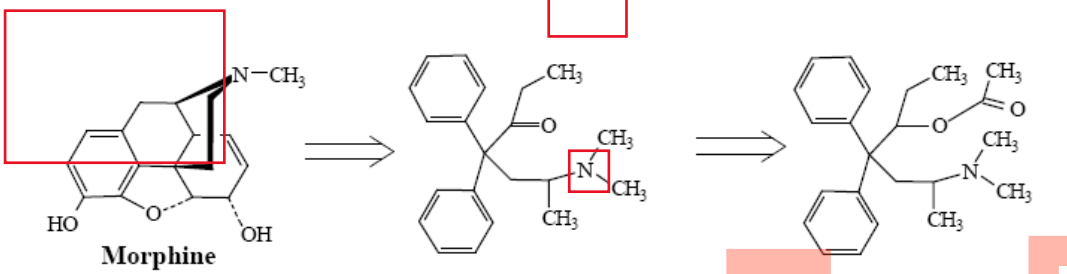
cis isomers (active): In commerical product



trans isomers (less active): Not in commerical product

VIII. Diphenylpropylamines: Methadone, Levomethadyl Acetate and Propoxyphene

This structural class of narcotic analgesics is essentially an acyclic version of the 4-phenylpiperidines. Methadone is a diphenylpropylamines with an additional propanone (ketone) side chain. Levo-α-acetylmethadol (LAAM) is a methadone analogues in which the ketone has been reduced to an alcohol and that alochol group esterified as an acetate ester.

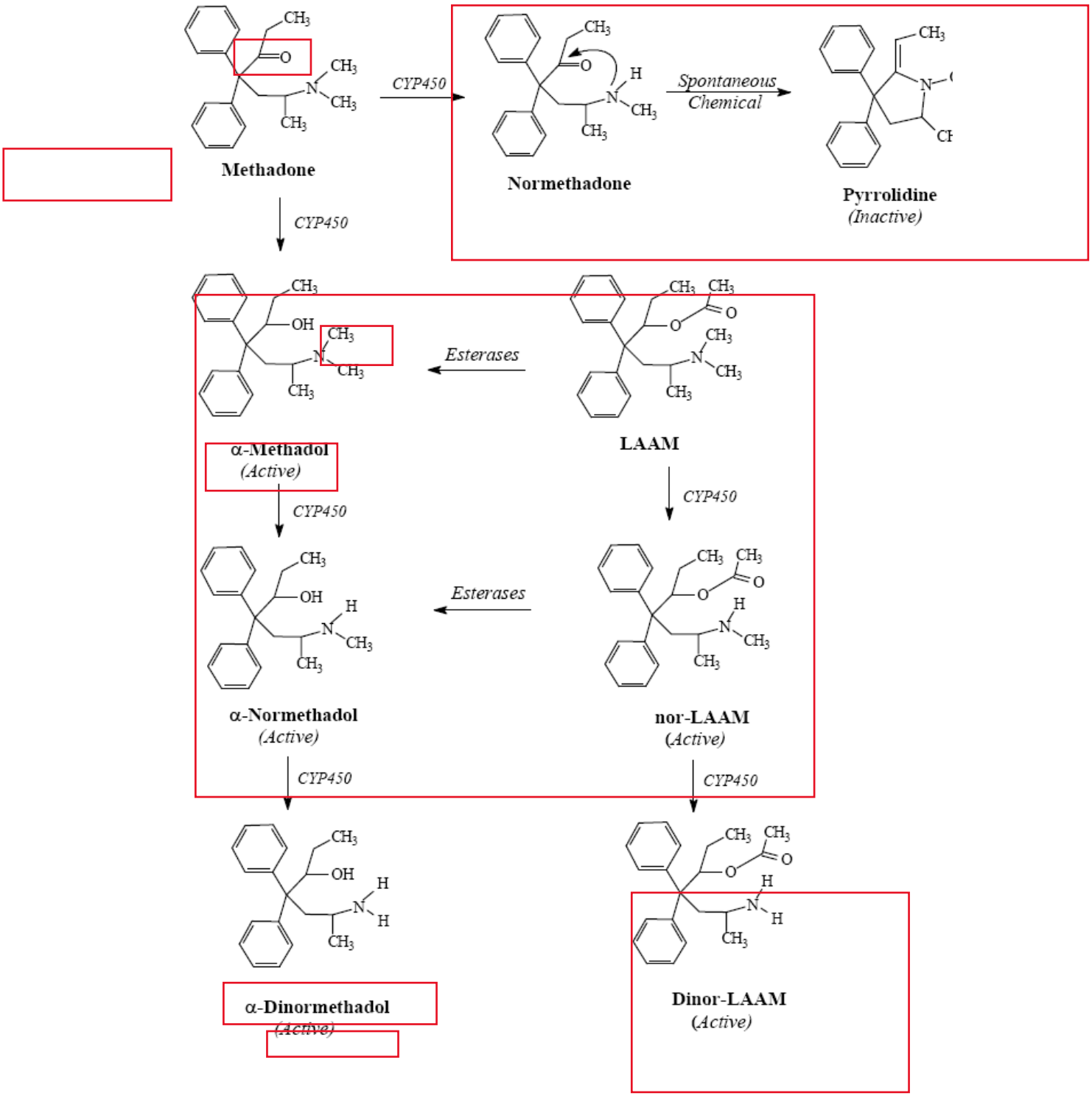


Morphine **Methadone: RP=1.0** **levo-α-Acetylmethadol**

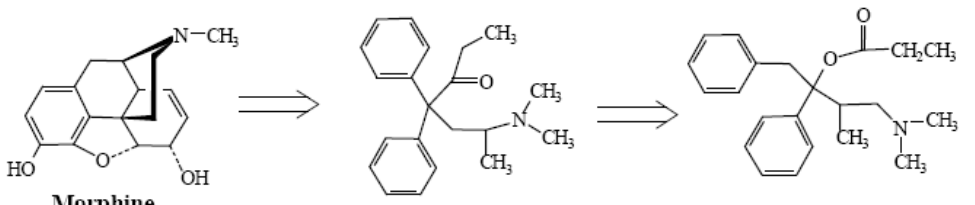
Methadone (Dolophine, Methadon) is chiral (carbon alpha to nitrogen) and is marketed as a racemate. The (-)-isomer is the active analgesic isomer. Methadone is very similar to morphine in its pharmacologic (mu agonist with RP = 1) and toxicologic profile except that methadone is highly effective after oral administration and has a much longer duration of action (19 hours). The extended and variable duration of action (15-40 hours)results in part from the formation of a number of active metabolites as shown below. Methadone is marketed as the HCl salt for oral administration. Methadone is commonly used for maintenance therapy of narcotic addicts.

Levo-α-acetylmethadol (LAAM) is similar in structure , pharmacology and pharmacokinetic properties to methadone. LAAM is approved to treat heroin withdrawal. Note that levo-α-acetylmethadol and methadone are "metabolically related" giving rise to several common, active analgesic metabolites. As a result LAAM has a relatively slow onset and very long duration of action (72-96 hours). The nor-LAAM and dinor-LAAM metabolites shown below are more potent than the parent compound and achieve higher plasma levels than the parent compound during prolonged therapy.

Metabolism of Methadone and LAAM



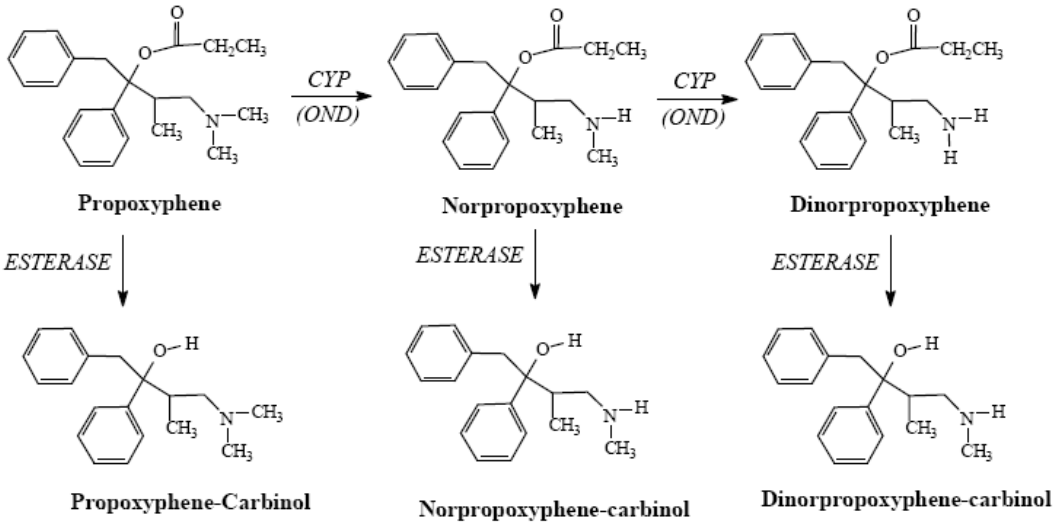
Propoxyphene (Darvon, Dolene) also is a diphenylpropylamine analgesic. Propoxyphene is marketed as a racemic mixture and the (+)-isomer is active as a mu agonist. It is nearly ten-times less active than morphine as an analgesic and is somewhat effective in alleviating mild to moderate pain. This compound reportedly has less abusive potential than codeine.The (-)-isomer has antitussive activity.



Morphine **Methadone: RP=1.0** **Propoxyphene: RP=0.12**

Propoxyphene is marketed as the HCl and napsylate salt (Darvon-N). The napsylate is available as tablets and an oral suspension.These products have higher oral bioavailability than morphine.

Propoxyphene is metabolized by cytochrome-mediated oxidative-N-demethylation to norpropoxyphene which issubstantially less active. Norpropoxyphene may undergo further OND to yield Dinorpropoxyphene and cyclic-dinorpropoxyphene. Propoxyphene and it's nor- and dinor-metabolites also undergo esterase hydrolysis to yield the carbinol metabolites. Propoxyphene and its nor-metabolites also undergo aromatic hydroxylation to yield the phenolic metabolites: All of these metabolites are reportedly less active than the parent drug.



Propoxyphene **Norpropoxyphene** **Dinorpropoxyphene**

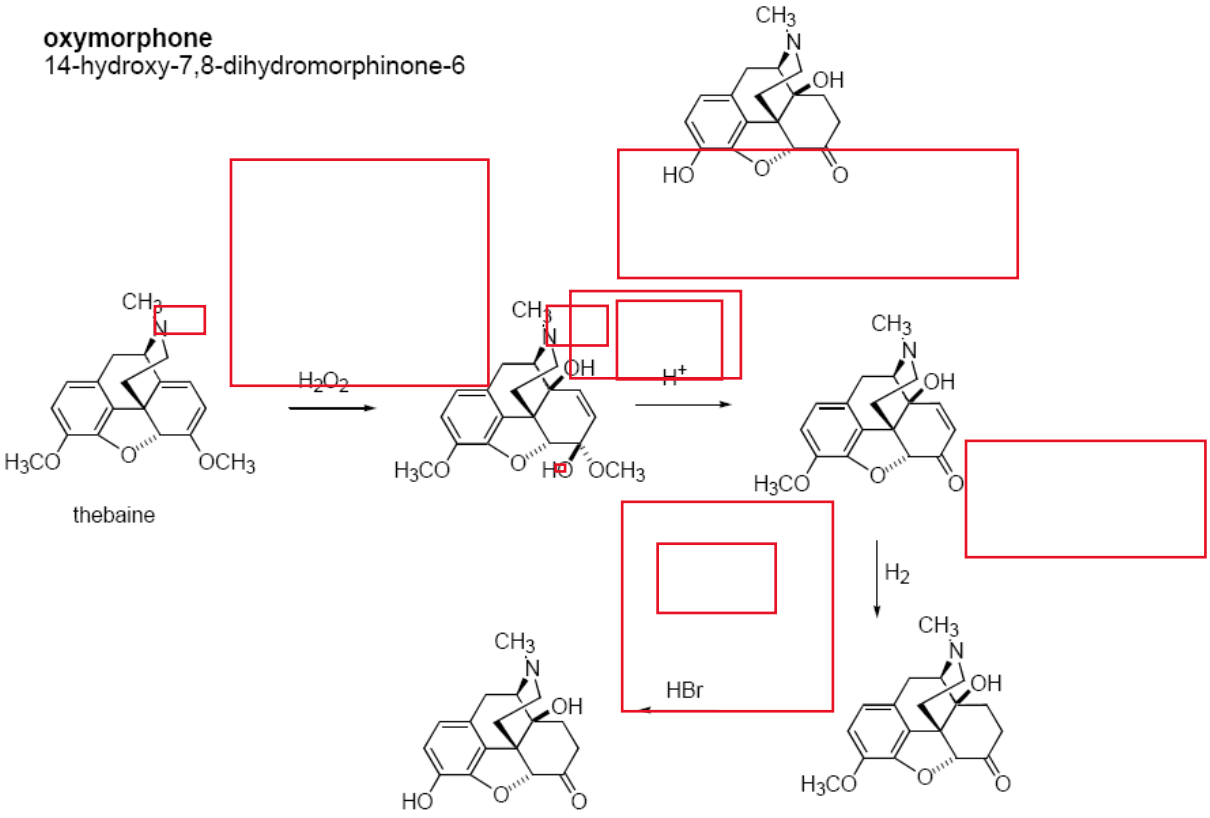
Propoxyphene-Carbinol **Norpropoxyphene-carbinol** **Dinorpropoxyphene-carbinol**

Summary of the opiate receptor binding profiles of the opioid drugs

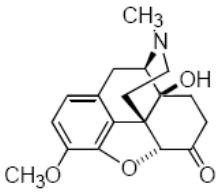
Opioid	μ	δ	κ	σ
Leu-enkephalin	+	+++		
Met-enkephalin	++	+++		
Morphine	+++	+	++	
Codeine	+	+	+	
Etorphine	+++	+++	+++	
Fentanyl	+++	+		
Sufentanil	+++	+		
Penatzocine	-	+	(++)	+
Nalbuphine	-	+	(++)	+
Nalorphine	--	(++)	(++)	+
Buprenorphine	(+++)			
Antagonists				
Naloxone	---	--	--	
Naltrexone	---	--	--	

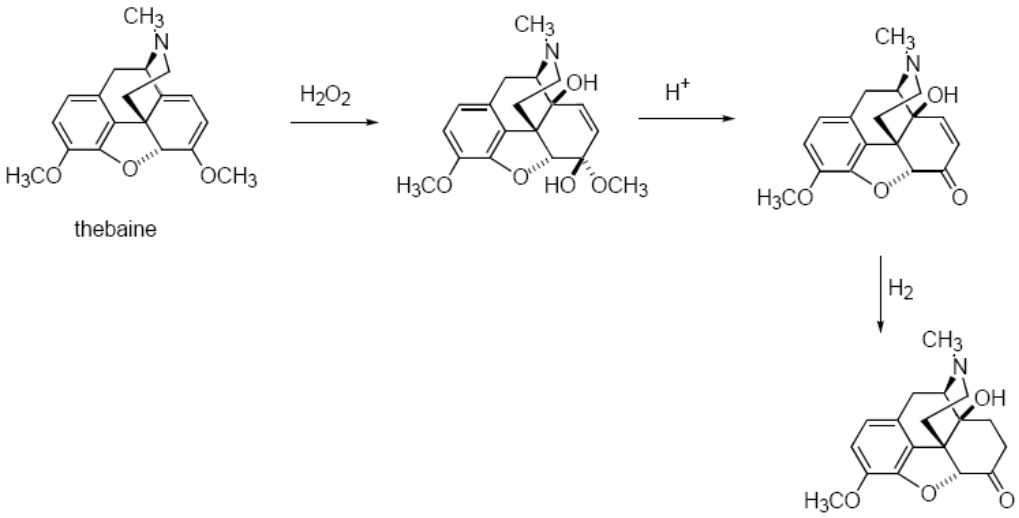
+ agonist, - antagonist, (+) partial agonist

ج



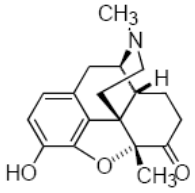
oxycodone
14-hydroxy-3-methyl-7,8-dihydromorphinone

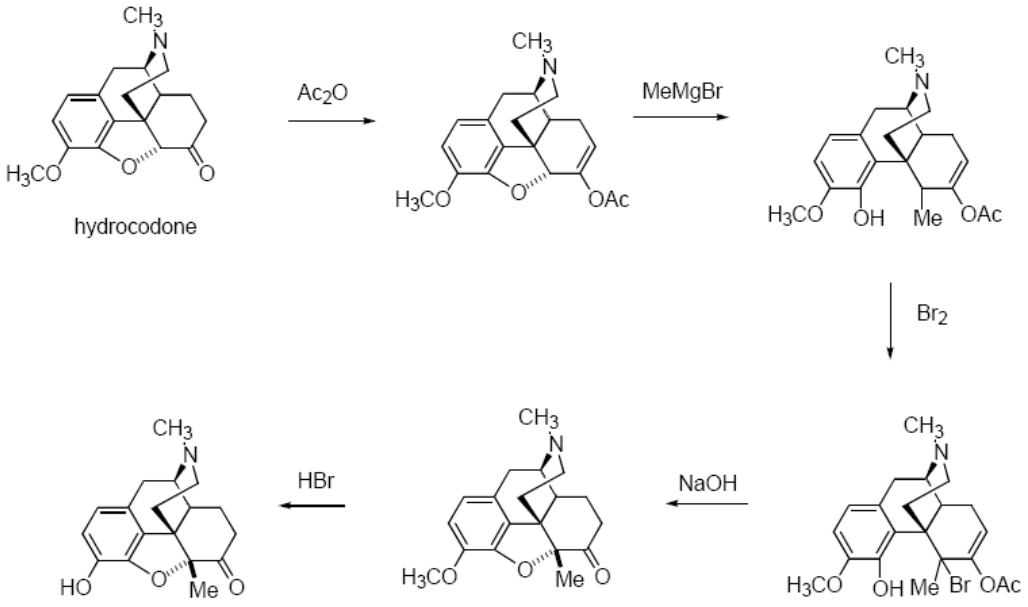




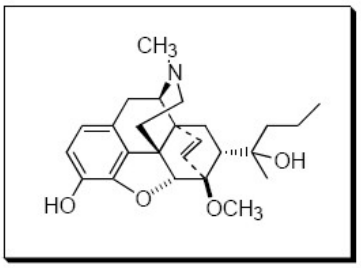
thebaine

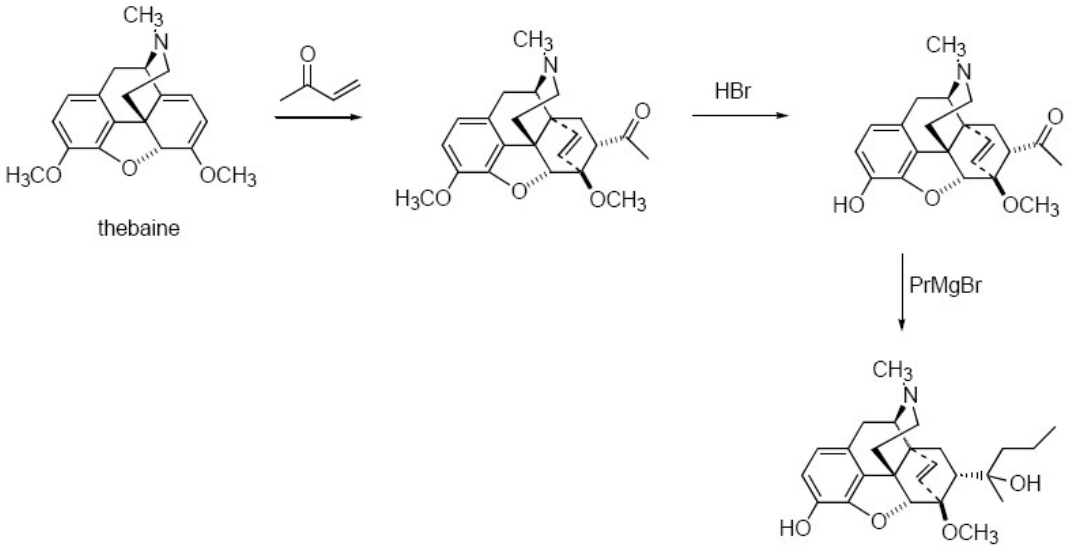
metopon
5-methyl-7,8-dihydromorphinone-6





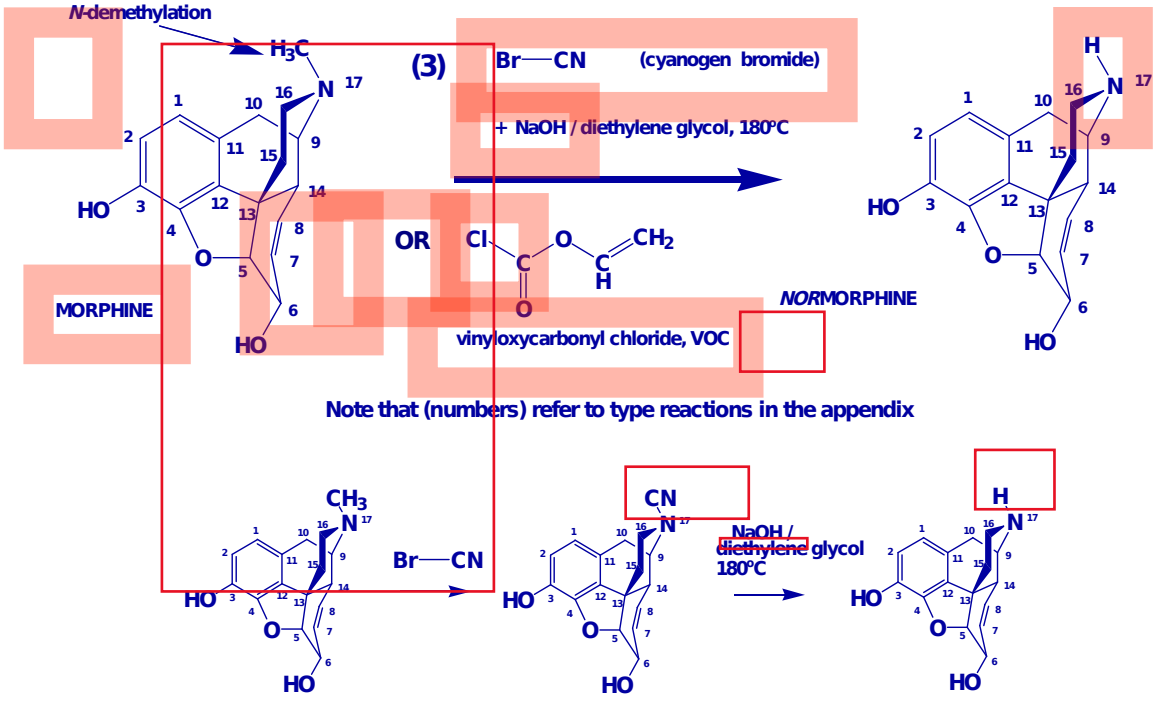
Etorphine


CH3
N
OH
HO
O
OCH3


CH3
N
H3CO
O
OCH3
thebaine
O
CH3
N
H3CO
O
OCH3
HBr
CH3
N
O
HO
O
OCH3
PrMgBr
CH3
N
OH
HO
O
OCH3

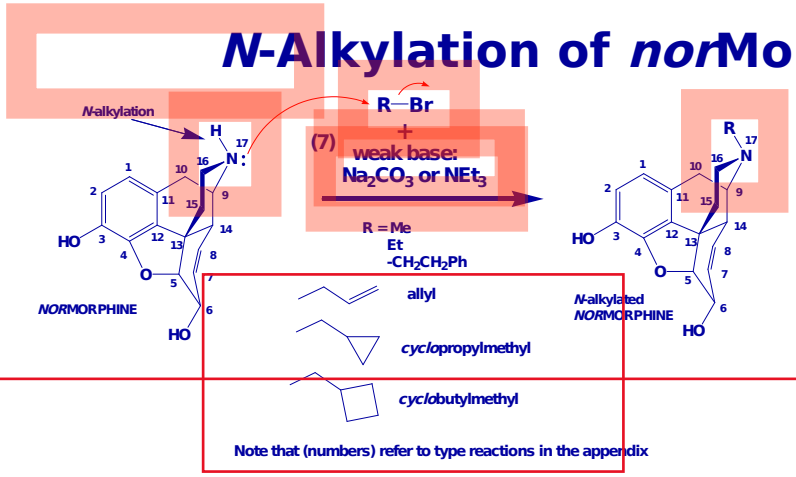
N-Demethylation of Morphine

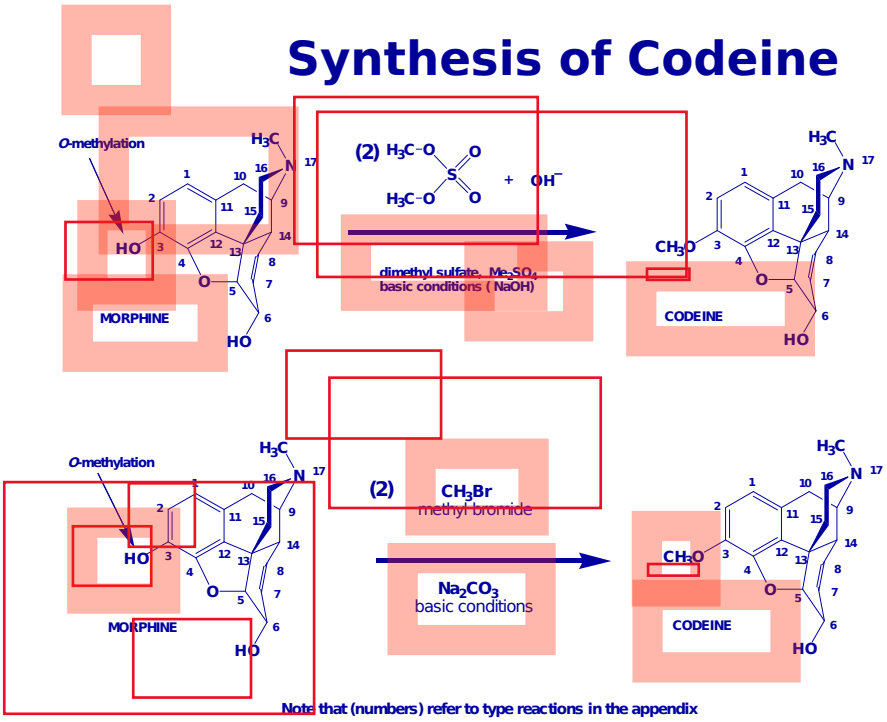
Appendix

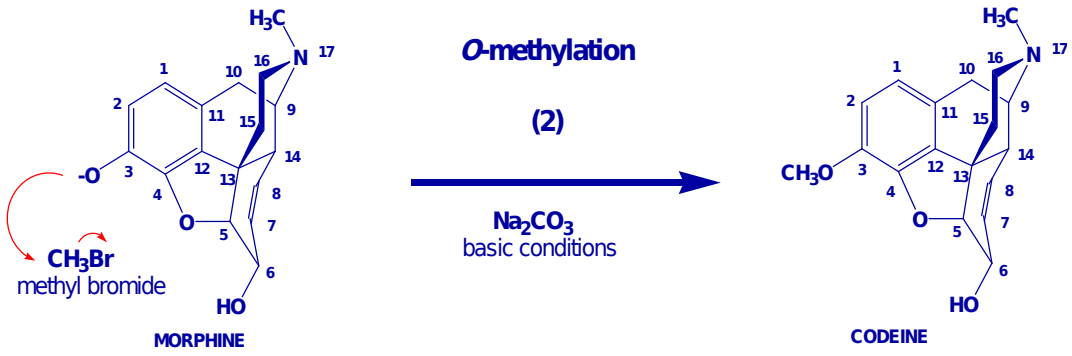


Appendix

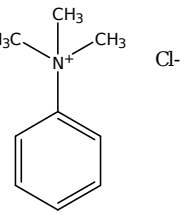
N-Alkylation of *nor*Morphine



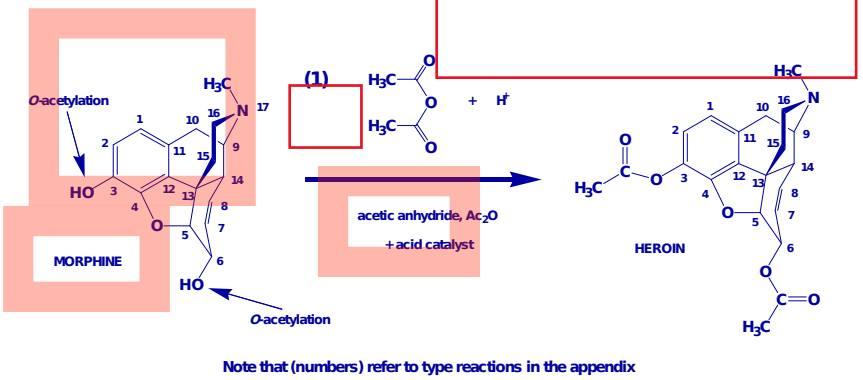




.Commercially trimethyl-phenyl-ammonium chloride is used

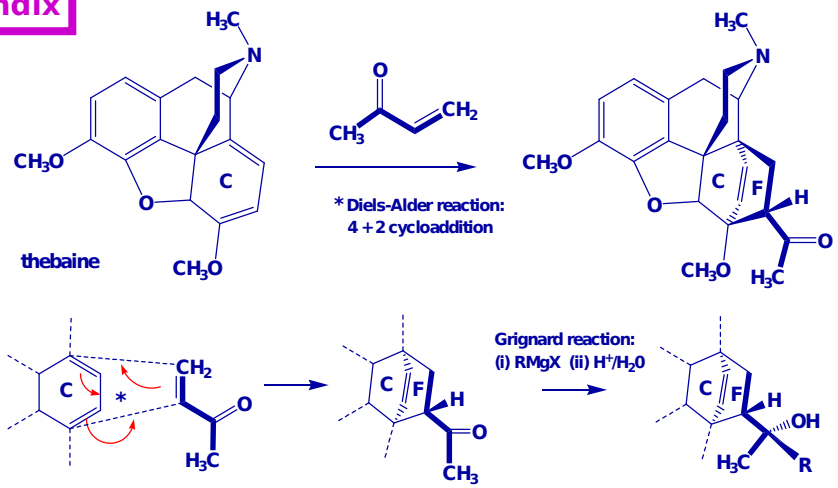


Synthesis of Heroin (Diamorphine)



Note that (numbers) refer to type reactions in the appendix

Appendix



Diels-Alder reaction between **thebaine** and **methyl vinyl ketone** adds an **extra ring, F**

the resulting **ketone** can be converted to a **tertiary alcohol** using a **Grignard reaction**

/http://www.opioid.umn.edu

Synthesis of Etorphine (Immobilon)